



CRIA UPDATE

COMMUNITY RESEARCH INITIATIVE ON AIDS

VOL. 10 No. 4

HIV Drug Resistance and Drug-Resistance Testing Just the FAQs

by Tim Horn

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Just when everyone starts getting used to viral load tests, with all their confusing “logs” and “copies” and “undetectable levels,” another family of lab tests with its own bewildering lingo arrives on the scene. Drug-resistance tests are, in fact, the most sophisticated forms of technology to be incorporated into the routine care of people living with HIV. In order to make sense of what these tests are, how they work, and the information they provide, it’s necessary to understand why they are actually needed – to help demystify why HIV treatment sometimes fails and what can be done about it.

This article is based on a question-and-answer lesson plan used by CRIA to help people living with HIV and service providers better understand HIV drug resistance, the most common and frustrating reason for treatment failure. As with all of the articles in *CRIA Update*, we encourage readers to use this information to communicate better with their healthcare providers. No question about drug resistance – including what you can do to help prevent it and the options you have if it occurs – is unimportant. We hope this review of frequently asked questions (FAQs) will help you and your healthcare provider decide when and how to use these tests and to make the most of the results they yield.

What is drug resistance?

- Many germs can enter the human body and cause harm, including viruses, fungi, bacteria, and protozoa. Once inside your body, the primary goal of a germ is to survive and reproduce.
- Most pharmaceutical drugs are designed to kill these germs or prevent them from reproducing. If a germ continues to reproduce during treatment, it can alter itself – or mutate – to avoid the drug. This is called drug resistance.
- When drug resistance occurs, the drug – or combination of drugs – can’t keep the germ from reproducing. Over time, the treatment can stop working completely.

How does HIV drug resistance occur?

- HIV drug resistance means a loss in the ability of a drug – or combination of drugs – to block HIV reproduction in the body.
- Drug resistance occurs due to mutations in HIV’s genetic structure, which is in the form of RNA, a tight strand of proteins needed by the virus to infect cells and produce new virus.
- HIV reproduces very rapidly and can’t correct mistakes made during the copying of genetic material, so mutations are very common.

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Survey
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This issue of CRIA Update goes to press the week of the terrorist attack. The enormity of the disaster and its potential implications are just beginning to sink in. Over the twenty years of the AIDS epidemic, many of us at CRIA have suffered seemingly unendurable losses. Yet, somehow we have found ways to endure those losses and, hopefully, grown in ways that allow us to offer something of value to our communities. As we struggle with further loss and our own fragile emotions, CRIA hopes for peace in the hearts of our readers, our communities and the world. We extend our deepest condolences to the friends and families of those who died in the violence of September 11, 2001.

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CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. CRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *CRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call Judy Codrington at 212-924-3934 ext. 121.

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Serostim® for HARS

CRIA has begun enrollment on this multicenter study that follows-up on a national level a previous pilot study that CRIA sponsored and conducted. This current 26-week, double-blind, randomized, placebo-controlled study looks at the effectiveness and safety of Serostim® (human growth hormone) when used to treat the abnormal fat distribution that occurs in patients treated with antiviral drugs for HIV infection. Patients with the condition know as HARS (HIV-related adipose redistribution syndrome) often have increased amounts of fat in the abdomen, the upper back, and (especially in women) in the breasts. If you are an adult who is HIV+, are on a stable anti-HIV drug regimen, and have problems with abnormal fat distribution, you may be eligible for the study.

Vigilance II Genotyping Study

The purpose of this study is to determine if an HIV-1 RNA genotype report is effective and safe to use for choosing therapy for HIV infection. We will be gathering data regarding an experimental test called genotyping, in this case the TruGene® HIV-1 Assay, developed by Visible Genetics Inc. Genotyping may allow doctors to see which drugs may or may not work against HIV infection. It may tell you if HIV may be resistant to certain drugs. Resistance means that the drugs given to you for your HIV may not work as well as thought. Genotyping is still being studied as an aid in treating HIV infection.

You may be eligible for this study if: 1. you are an HIV-1 infected person with a viral load of greater than or equal to 1,000 copies/mL 2. you and your doctor have determined that a change in your anti-HIV therapy is indicated; or if no prior therapy has been given for HIV-1, then you and your doctor agree that therapy needs to be started.

You will come in for one blood draw specifically for the study. This blood will be used for the genotyping test. Your personal doctor will get the results of the genotyping test within 7-10 business days and use these results to help choose a drug regimen that may be beneficial to you. We will gather data about your progress (up to one year) from later blood draws by your personal doctor that are part of your regular care. You will be paid \$15 after enrolling into the study to cover transportation, lost time from work, or meals. Your insurance company or a state health insurance agency will be billed for the blood tests. If you do not have insurance or state coverage and if you cannot pay for the tests, your study doctor will try to enroll you in a special patient assistance program.

For more information on these studies, please call
Dr. Douglas Mendez at (212) 924-3934, ext. 126
or visit our Web site:
www.criany.org

Editor's Notes

- All material in CRIA Update is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
- CRIA Update refers to all drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.

Just the FAQs

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- Two of the most important HIV enzymes are reverse transcriptase and protease.
- Nucleoside analogues and non-nucleoside reverse transcriptase inhibitors target the reverse transcriptase enzyme, while protease inhibitors target the protease enzyme.
- In order for these antiretroviral drugs to be effective, they must attach themselves to the necessary enzyme. Certain mutations can prevent a drug from binding with the enzyme and, as a result, make the drug less effective.

How do mutations occur before starting therapy?

- **Natural selection:** Soon after HIV enters the body, the virus begins reproducing at a rapid rate – billions of new viruses are produced every day. In the process, HIV produces both perfect copies of itself (wild-type virus) and copies containing errors (mutated virus). In other words, there is no single virus in the body but, instead, a large population of mixed viruses called quasispecies.
- Wild-type virus is the most natural and usually most powerful form of HIV and, as a result, reproduces the best. Before therapy is started, wild-type virus is the most abundant in the body and dominates all other quasispecies.
- When HIV makes mistakes during copying, mutated viruses – called variants – are produced. Some variants are too weak to survive and/or can't reproduce. Others are strong enough to reproduce but still can't compete with the more fit wild-type virus. As a result, their numbers are less than wild-type virus in the body.
- Some variants have mutations that allow the virus to partly, or even fully, resist an antiretroviral drug. This is why people living with HIV should never take just one antiretroviral (monotherapy). For example, HIV only requires one mutation to become completely resistant to Efavirenz (EFV). Similarly, a single mutation can cause resistance to all of the non-nucleosides.
- These mutations occur randomly and there's no known way to prevent them. Variants usually don't go on to develop additional mutations; doing so compromises their ability to stay alive in the body. So, while these variants may be completely resistant to one drug, they're almost always sensitive to other drugs in a regimen. This is why three-drug combinations work better: a variant may be resistant to one of the drugs but doesn't stand much of a chance when facing two other drugs that bind to different parts of the virus.
- **Transmission of drug-resistant virus:** According to some studies, between 10% and 30% of all new HIV infections (people infected within the past two years) involve strains resistant to at least one drug.

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- Many HIV-positive people now take or have taken antiretroviral therapy. If someone who has developed resistance to one or more of the antiretrovirals transmits the virus to someone else, their partner could now have a multiple-drug-resistant (MDR) variant of HIV.
- If this person were to start therapy later on with any of the antiretrovirals that the first person had developed resistance to, it might be difficult to reduce viral load or keep viral load undetectable.

How do mutations occur during therapy?

- Soon after antiretroviral therapy is started, the amount of virus in the body is reduced dramatically. Unfortunately, no combination completely stops HIV from reproducing. There's always a small population of virus that continues to reproduce.
- Therapy reduces the amount of all HIV quasispecies in the body. The amount of wild-type virus is dramatically reduced, as is the number of variants.
 - Because wild-type virus is usually the most sensitive to antiretrovirals, HIV variants in the body may have a survival advantage. In the presence of therapy, variants can become the dominant strain of HIV, even though there is much less virus in the body.
 - Over time, variants accumulate additional mutations. Some of these mutations will harm the virus, while others will further limit a drug's ability to block reproduction. Once the virus has accumulated enough mutations, the drugs lose their ability to bind to it and prevent it from reproducing. As the drugs become weaker, the amount of drug-resistant virus in the body increases. An undetectable viral load can become detectable again and increase over time. If the drug-resistant virus continues to reproduce, it can acquire even more mutations to resist the antiretrovirals completely.
- Mutations that emerge during therapy can be divided into primary mutations and secondary mutations. Each antiretroviral is associated with at least one primary mutation. Primary mutations cause the greatest amount of drug resistance. Secondary mutations don't cause drug resistance unless a primary mutation is present. If both primary *and* secondary mutations are present, drug resistance becomes more complicated.
- Primary and secondary mutations usually have a negative effect on the power of the virus. This is why some people who experience an increase in their viral load might not see a decrease in their CD4+ cell counts, at least not at first. In other words, the virus may lose its ability to cause damage to the immune system if it contains drug-resistance mutations. However, studies show that some mutations can cause the

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virus to regain its power and possibly become even more powerful than wild-type virus.

- Cross-resistance can also occur during therapy. When HIV becomes resistant to one drug, it can automatically be resistant to other drugs in the same class. For example, the primary and secondary mutations that occur in someone who is taking the protease inhibitor Crixivan (indinavir) are the same mutations that cause resistance to Norvir (ritonavir). Even though the person hasn't taken Norvir, he or she will likely be cross-resistant to the drug and probably wouldn't benefit from it.
- The key to avoiding the accumulation of mutations that cause resistance and cross-resistance is to keep the amount of virus in the body as low as possible, for as long as possible.

What factors contribute to the accumulation of drug-resistance mutations during therapy?

- Don't forget the golden rule: the less virus there is in the body, the less likely it is that mutations will develop. A powerful regimen is the most effective way to keep the level of virus low – preferably undetectable – and to delay additional mutations from occurring.
- There are a number of factors that can prevent your regimen from being as powerful as it can be:
- **Poor adherence:** For drugs to work correctly, they must be taken exactly as prescribed. This means taking the correct number of pills each day, being careful to take them a certain number of hours apart, while also following dietary requirements.
- Skipping doses or taking medication incorrectly can cause the trough level of a drug to decrease in the body. The trough level is the amount of drug left in your body just before another dose is taken. If the trough level becomes too low, HIV can reproduce more freely and accumulate additional mutations.
- According to a few research reports, an HIV-positive person must be more than 95% adherent with his or her regimen in order for it to continue working properly. This means missing less than one dose a month.
- **Poor absorption:** Not only must antiretrovirals be taken on schedule, they also need to be absorbed effectively into the bloodstream. A drug – or combination of drugs – that isn't absorbed properly can result in trough levels that are too low and, ultimately, allow HIV reproduction and the accumulation of drug-resistance mutations.
- Some drugs have specific dietary requirements. For example, people taking standard doses of Crixivan must take the drug every eight hours on an empty stomach. This means not eating within two hours before or one hour after taking the drug. (Note: If Crixivan is taken in combination with Norvir, food restrictions don't apply.) Conversely, Fortovase (saquinavir) should be taken with food, preferably food containing a moderate amount of fat. If dietary requirements aren't followed, drug levels in the body will decrease.

- Diarrhea and vomiting can cause medications to be expelled from the gut too quickly, reducing the amount of drug absorbed into the bloodstream.
- **Varying pharmacokinetics:** Pharmacokinetics is a term used to mean how a drug is absorbed, distributed, metabolized, and removed from the body.
- Even though two people might receive the exact same dose of a drug, the amount of drug may be higher in one person's bloodstream than in the other's bloodstream. Factors such as body weight, height, age and gender can contribute to this difference. Some people also process, or metabolize, drugs faster or slower than others do. This can speed up – or slow down – the rate at which a drug is cleared from the body.
- A drug's correct dose – the dose dispensed by pharmacists – is the average dose found to be safe and effective in clinical trials. In other words, some people may be able to keep their viral load undetectable using lower doses of the drug, while others might require higher doses.
- In the future, healthcare providers may perform blood tests to measure the amount of drug in their patients' bodies. This is called therapeutic drug monitoring and it may help determine whether or not you have the correct trough level of each medication.

Does a rebound in viral load mean that drug resistance has occurred?

- Figuring out if a regimen isn't working properly can be determined in three ways:
 - 1) A viral load that fails to go undetectable within the first few months of therapy.
 - 2) A viral load that goes from being undetectable to detectable (note: a one-time "blip" in viral load isn't usually a sign that a drug regimen is no longer working).
 - 3) A detectable viral load continues to increase, even though you're still on therapy.
- While a viral load test can help determine whether or not a regimen is still working correctly, it can't explain *why* a regimen is no longer working the way it should.
- A detectable or increasing viral load doesn't necessarily mean that drug-resistance mutations have developed. It may be due to poor adherence or poor absorption. While these can eventually lead to the emergence of drug-resistance mutations, viral load can become detectable before they develop. It's important to determine the reason why viral load is increasing soon after it becomes detectable.
- If resistance mutations have developed, viral load tests can't determine whether or not the virus is resistant to one specific drug or the entire regimen. Moreover, if you have drug-resistant HIV, viral load testing can't determine which drug or combination of drugs is likely to be the most effective in the future.
- There are two tests, or assays, that look for drug resistance. Genotypic testing can help determine whether specific mutations

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Resistance Testing: A Look at the Data

by Ben Cheng

Resistance testing is fast becoming part of standard of care for treating people living with HIV. It is yet another tool, along with viral load and CD4+ cell counts, to optimize the selection of anti-HIV therapies. Several past studies have shown that people using resistance tests to choose a regimen were more likely to achieve undetectable viral loads and have prolonged anti-HIV responses compared to people who chose a regimen simply based on viral load, CD4+ counts and their treatment history. Other studies have not shown a better result for people who used resistance tests. Now, several more recent studies show the complexities in interpreting the results of these tests and make it clear that some fine-tuning in interpretation is still required.

Genotypic Resistance Testing

Results from three separate studies illustrate the benefits of genotypic testing. The French Viradapt study followed 108 people, all of whom had previously taken anti-HIV therapies and had viral loads over 10,000 copies. Half of the participants received the best available therapy based on their previous treatment history, while the other half received the best available therapy based on results from a genotypic test. Neither group knew how treatment decisions were made for them. At the end of six months, those whose treatment decisions were based on the genotypic test experienced a more significant drop in viral load and were more likely to achieve undetectable viral loads compared to those who didn't get a resistance test (32% versus 14%).

The GART study, which was conducted in the United States, had very similar results. This study included 153 people, all of whom had experienced a return of measurable viral load while on a three drug regimen that included a protease inhibitor. Half of the participants chose a new regimen based on a genotypic test with expert interpretation. The other half selected a new regimen based on previous anti-HIV therapy history. After 12 weeks

of the study, there was again a significant difference in response, favoring the group receiving the resistance test with expert interpretation.

The third genotypic testing study was conducted in Spain and known as the Havana Trial. This study was slightly different from Viradapt and GART. It included 274 participants, all of whom had been on prior anti-HIV therapies. Although participants were randomly assigned to receive either genotypic testing or no testing, they were also randomly assigned to receive either expert advice or no advice in helping to choose a new regimen. In other words, some of the par-

“Several more recent studies... make it clear that fine tuning in interpretation of [resistance tests] is still required.”

participants received both resistance testing and expert advice, some received neither, and the remainder received only resistance testing or expert advice. The expert advice was given by a group of leading virologists and clinicians. At the end of the six month study, 58% of people receiving genotypic test information had undetectable viral loads compared to 42% of those who did not. People who received expert advice were also more likely to have undetectable viral loads compared to people who didn't get expert advice (59% versus 41%). Not surprisingly the group that received both genotypic testing and expert advice had the best overall response, with 69% having undetectable viral loads compared to 36% of those who received neither intervention.

This study shows the importance of expert advice and its added benefit to resistance testing.

Phenotypic Resistance Testing

Results from a study known as VIRA3001 and conducted by Virco, developers of one of the phenotypic resistance tests, show the benefit of phenotypic testing. This study followed 273 people, all of whom had taken a three drug regimen containing a protease inhibitor and had viral loads above 2,000 copies. Almost all of the participants had taken Efavir (3TC) and AZT, and the majority had also taken Zerit (d4T). Additionally most of the participants had taken either Viracept (nelfinavir) or Crixivan (indinavir). Half of the participants made treatment decisions based on information from a phenotypic test while the other half made decisions based on treatment history. After 16 weeks of the study, people receiving the resistance test were more likely to have undetectable viral loads (45% versus 34%) and a more pronounced drop in viral load compared to those who didn't receive the test.

The California Collaborative Treatment Group's CCTG 575 study compared phenotypic testing to no resistance testing. 238 people, all of whom had taken anti-HIV therapy for an average of about three years, participated in the study. Most of the participants had taken one protease inhibitor-based regimen (mostly either Viracept or Crixivan), and most had not previously taken a non-nucleoside reverse transcriptase inhibitor. This study found no difference in response rates between the two strategies - after one year, about 50% of the participants achieved viral loads below 400 copies and about 40% achieved below 50 copies. There may be several reasons for the lack of a difference seen in this study. Participants were generally not heavily pretreated and so had a lot of treatment options. Perhaps more importantly, the criteria used to determine resistance by the phenotypic test might have been flawed. As a result, participants

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who received the resistance test were far more likely to choose Zerit (d4T) and/or Videx (ddI) as part of their regimen because the test results showed that they were sensitive to these two drugs and that most were resistant to Ziagen (abacavir), whereas people without the resistance information were far more likely to choose Ziagen.

Since the start of this study, the field has rapidly evolved. We now know that there is significantly more cross-resistance (where resistance to one drug results in resistance to another) between AZT and d4T. Similarly, a smaller decrease in sensitivity to ddI than previously thought may result in the drug losing effectiveness, whereas the opposite may be true for Ziagen. As a result of this study, the criteria to determine resistance to ddI, d4T and Ziagen have been changed. Another study conducted in France, known as NARVAL, had similar findings and participants made similar treatment choices based on phenotypic resistance information.

Results from the CCTG study highlight the importance of establishing clinically relevant “cut offs” for the phenotypic tests to determine whether a particular drug will still be active against HIV (no resistance to the drug), whether it may have some moderate activity against HIV (low level resistance) or whether it isn’t expected to have any activity against the virus (high level resistance). To date, these clinically relevant “cut offs” have only been established for two drugs, Ziagen and Kaletra (lopinavir), although it is likely that others, including ddI, d4T and tenofovir, may be established before the end of the year. To further add confusion to the matter, these “cut offs” are likely to be different for the two phenotypic resistance tests that are currently available because Virco’s Antivirogram and ViroLogic’s PhenoSense use different technologies to measure phenotypic resistance.

Ben Cheng is Director of Antiviral Advocacy at Project Inform in San Francisco.

The Role of Resistance Testing in an Inner City Population

by Jason M. Leider, MD, PhD

The introduction of resistance testing technology into the clinical practice of HIV medicine has offered me and my providers at the North Bronx Health Care Network of Jacobi and North Central Bronx Hospitals an opportunity to revolutionize our approach to HIV treatment. In our practice, we provide care to more than 2,000 HIV-positive adults and children. Approximately 40% of these individuals currently maintain viral loads below the limit of detection of the viral load assay. Many of the remainder of our patients are treatment experienced, some extensively so, often having been on multiple previous regimens. Resistance testing has been an extremely helpful tool in guiding our treatment decisions for many of these patients.

Our Choice in Technology for Resistance Testing

As participants in an ambitious resistance research study, we have now performed resistance tests on more than 180 patients. Usually, we have used the genotype assay, rather than the phenotype assay. This preference for genotyping is based on faster turnaround time (1 to 2 weeks versus 2 to 4 weeks for phenotyping), lower assay cost, lack of impressive data to show superiority of phenotyping over genotyping, and a lack of data for the phenotypic resistance tests correlating drug

resistance in the lab with actual drug activity in people. Thus, we have used phenotyping for patients who have complex genotype results (for example, unusual NNRTI mutation patterns such as G190A/S, K101E, multiple PI mutations, or multiple NRTI mutations especially for patients with a history of being heavily pre-treated).

The Role of Resistance Testing in Practice

Currently, the Department of Health and Human Services’ Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (August 13, 2001) propose that resistance testing be used as follows:

Recommended:

- virologic failure (i.e., failure to achieve a viral load of less than 1000 copies/mL after more than 16-24 weeks of treatment)
- suboptimal suppression of viral load after initiation of treatment (i.e., less than 0.5-0.75 log₁₀ reduction in plasma HIV RNA by four weeks following initiation of therapy or more than 1 log₁₀ reduction by eight weeks)

Consider:

- acute HIV infection

Resistance Tests in Use

No resistance tests have been approved by the Food and Drug Administration (FDA) so far. There are a number of tests currently being used, however, and many health insurance plans cover them, including some state AIDS Drug Assistance Programs (ADAPs) and Medicaid Programs.

Genotype Tests

TRUEGENE HIV-1 Genotyping Kit (Visible Genetics, Inc.)

VircoGEN (Virco) (processed in US by LabCorp)

INNO-LiPA HIV-1 RT (Line Probe Assay) (Innogenetics)

HIV-1 GentyPR (Specialty Laboratories)

Phenotype Tests

PhenoSense HIV (ViroLogic, Inc.)

Antivirogram (Virco)

Not recommended:

- chronic HIV infection in treatment naïve patients
- after discontinuation of treatment for more than two weeks
- plasma viral load less than 1,000 HIV RNA copies/mL

We follow the recommendations of these guidelines for patients with virologic failure (especially first line failure), suboptimal suppression, and viral loads less than 1000 copies/mL, as resistance testing is not sensitive enough to accurately detect mutations for these patients. In our patient population, people rarely come into care during acute HIV seroconversion, so we have not had the chance to do genotyping for this patient group. Unfortunately, many of our patients first come to us with chronic HIV infection, often with CD4 counts less than 100.

It is for this latter group that we have deviated from the guidelines and performed resistance testing. Our rationale for using genotyping for this population is that many of our patients live in an area where their contacts have been treated with HIV therapy and may have transmitted drug-resistant virus. While we have only performed resistance testing on about ten naïve patients with chronic HIV infection, we have already seen one patient with a significant mutation in the protease inhibitor class prior to ever taking HIV medication. This patient had been HIV infected over five years ago and had maintained a CD4 count more than 500 and a viral load of about 50,000. However, he had fallen out of care for the past three years and now came back into care due to the development of severe rash, itching and weight loss. His CD4 had decreased to 3, while his viral load was now greater than 750,000. This serious decline in his health prompted us to send for a genotype, which revealed the mutation associated with loss of activity to Viracept (nelfinavir). The patient has now started HIV treatment, and the results of his genotype test definitely impacted on our choice of his initial HIV regimen.

We have also differed from the guidelines in performing resistance testing on pre-

treated patients who have discontinued therapy for more than two weeks. We have found that at least 30% of our patients harbor significant resistance mutations despite the interruption in therapy. Many of these patients have retained the K103N mutation associated with resistance to all of the medications in the NNRTI class. In fact, we have seen that NNRTI resistance tends to be persistent, with many patients showing this mutation despite having discontinued NNRTI treatment for more than six months. In light of this, we have found genotyping to be especially useful in helping us avoid prescribing inactive medications.

“NNRTI resistance tends to be persistent, with many patients showing [the K103N] mutation despite NNRTI treatment for more than six months.”

At our medical centers, we also care for many HIV-positive pregnant women. For these patients, we routinely perform genotype testing before starting HIV medication as it is imperative to design treatment regimens that offer the greatest chance of decreasing their viral load and avoiding maternal-fetal transmission of HIV. The following patient illustrates the value of using resistance testing in this situation. One of our heavily pre-treated patients is now twelve weeks pregnant. Her genotype, done six months ago when her CD4 was 31 and her viral load was 3,496, revealed many significant mutations to virtually all of the medications in the NRTI class as well as high level resistance to medications in the NNRTI and PI classes. Despite this result, she decided not to change her regimen and continued taking Zerit (d4T), Epivir (3TC), Norvir (ritonavir) and Crixivan (indinavir). In the interim, she has had several hospitalizations for psychiatric

causes, fragmenting her HIV outpatient care. She returned to care with a CD4 count of 9 and a viral load that had increased to 22,000. We repeated her genotyping and have discovered a genotype showing less severe mutations in the NRTI class, the same NNRTI mutations and no mutations in the PI group. The patient later revealed to us that she had a problem obtaining her HIV medications

and has not taken them for more than two weeks. Without the genotype from six months ago, we may have designed a regimen of inadequate NRTI or PI potency. Having serial genotypes for this patient is invaluable as we can now design a regimen with the greatest potential for virologic success.

Conclusion

In conclusion, we have found resistance testing to be a welcome addition to our clinical practice. Due to the need for rapid results, we have used genotyping initially for resistance evaluation and have reserved phenotyping for interpretation of the most complex patients. The extensive penetration of treatment into our community has made genotyping a helpful tool for guiding treatment decisions for patients who are failing current therapy as well as for chronically infected naïve patients. Pregnant women are a group of patients in which we feel genotyping definitely has a niche for ensuring intelligent treatment decisions. Of note, as NNRTI therapy becomes a more common treatment option for HIV+ pregnant women - specifically the use of Viramune (nevirapine) - we anticipate that many women treated with Viramune during pregnancy will eventually develop NNRTI resistance. Repeat resistance testing of these women, should they experience future treatment failure, will be of increasing importance to guide treatment decisions. As can be imagined, it will also be necessary to genotype these same women who in the future have subsequent pregnancies should they have detectable viral loads.

Jason M. Leider, M.D., Ph.D., is Director of the Adult HIV Service for the North Bronx Health Care Network of Jacobi and North Central Bronx Hospitals.

New Drugs in Development

Very Viread

Like stepping onto the bathroom scale the day after Thanksgiving, viral load assays and drug-resistance tests have an annoying habit of telling the truth when we least want to hear it. Finding out that your virus is resistant to the antiretroviral drugs you are taking, even though you've been doing your best to take them correctly and on time every day, can be a real slap in the face. This is especially true if you've gone through many of the drugs that are currently available. When you factor in cross resistance between these drugs – including all of the available non-nucleoside reverse transcriptase inhibitors (NNRTIs) and most of the protease inhibitors (PIs) – that can further limit your options, finding a new combination of drugs can prove to be a real challenge.

Until there's a cure for this dreaded disease, new drugs with unique resistance profiles will always be needed to help patients with limited treatment options stay one step ahead of the game. There are many HIV-positive people out there who are no better off than people living with HIV in the mid-1980s – with no options to currently choose from, the only possibility is to wait for a modern-day AZT to become available through either a large clinical trial, an expanded access program, or full-fledged approval by the U.S. Food and Drug Administration (FDA). Realistically speaking, adding a new drug that becomes available to “intensify” a last-resort regimen that is no longer working correctly is the only option available to a growing number of HIV-positive people. Thus, whatever becomes available had better be worth the wait.

One of the most eagerly awaited drugs is tenofovir disoproxil fumarate (Viread), Gilead Science's leading anti-HIV contender, to be reviewed by the FDA on October 3rd. While its once-daily dosing schedule will undoubtedly be alluring to folks who are still picking and choosing their first antiretroviral drug regimen, Viread's crowning glory appears to be its ability to intensify the antiviral effect of regimens that are no longer able to keep viral load undetectable – good news for patients who don't have much to choose from.

Technically speaking, Viread represents a new class of drugs being studied to treat HIV: nucleotide reverse transcriptase inhibitors. The truth is, nucleotide analogues are very similar to current nucleoside analogues (e.g., Retrovir, Zerit, and Epivir). The only difference is that nucleotide analogues, unlike nucleoside analogues, are chemically pre-activated and thus require less biochemical processing in the body for them to become active.

So far, so good: Viread only needs to be taken once a day (300 mg tablets) and its side effects – including nausea, vomiting, headaches, and increased blood pressure – are usually only temporary. While tenofovir can cause increases in blood levels of creatinine, an enzyme related to kidney function, the drug does not appear to cause the serious kidney problems seen in earlier studies of adefovir (Preveon), Gilead's first nucleotide analogue rejected by the FDA in November 1999. What's more, because Viread is broken down by the kidneys and not the liver, it's not likely that it will interact with other antiretroviral medications; the only interaction thus far has

been a 50% reduction in delavirdine (Rescriptor) blood levels.

It's best to take Viread with food, preferably a meal containing a sizeable percentage of fat. Doing so increases the amount of Viread in the bloodstream, a significant advantage for folks hoping to squeeze as much benefit out of the drug as they possibly can.

As for tenofovir's resistance profile, the drug is active against strains of HIV resistant to AZT (Retrovir), ddI (Videx), ddC (Hivid), 3TC (Epivir), and abacavir (Ziagen). Tenofovir is also active against virus containing the sinister Q151M mutation – a single mutation that results in high-level resistance to multiple nucleoside analogues.

One of the most important clinical trials of Viread has been GS 902, a phase II study that randomly assigned 189 HIV-positive people to add one of three doses of Viread (75 mg, 150 mg, or 300 mg) or placebo to their current regimen. Depending on your point of view, this was a highly peculiar study design. Most clinical trials offer volunteers a whole new batch of currently approved drugs with the possibility of also getting the experimental compound. But for the volunteers enrolled in this study, coming up with two or three new drugs to combine with Viread was almost impossible – the majority of patients had been receiving HAART for at least four years prior to entering the study and had already gone through many of the approved options available to them. All of the patients in GS 902 had detectable viral loads (between 400 and 100,000 copies/mL) when they enrolled in the study, meaning that their virus was no longer responding

by Tim Horn

to the “salvage” regimen they were currently taking. In this way, the results of GS 902 would reflect what people with drug-resistant virus might expect in the real world – would the addition of a single new drug to an already failing regimen offer significant help to patients who don’t have other options to choose from?

Upon entering the study, approximately 94% of the patients had resistance to at least one nucleoside analogue, with more than 71% of the patients resistant to AZT. The average viral load at study entry was between 5,000 and 6,000 copies/mL and the average T-cell count was 375 cells/mm³. After 24 weeks in the study, patients receiving the 300 mg daily dose of Viread had reduced their viral load by 75% (0.58 log), compared to almost no change among patients who received placebo. After 48 weeks, viral load had been reduced by almost 80% (0.62 log) in patients originally randomized to receive the 300 mg dose of tenofovir. Encouraging results indeed.

While Viread worked well for patients who were resistant to any of the nucleoside analogues prior to entering the study, it’s still not clear which mutations are actually caused by this drug. In one recent analysis involving 135 patients who have been taking 300 mg daily Viread in combination with their previous regimen for at least 96 weeks, only 21 (15.5%) have seen their viral load increase to levels above and beyond where they were prior to adding the nucleotide analogue. In these 21 patients, new mutations conferring additional resistance to their current PI(s), NNRTI, or nucleoside analogues were found – which might explain the increase in

viral load – but none developed any tell-tale mutations that have been shown in test tube studies to be associated with resistance to Viread. In other words, Viread may still have been chugging away as the other drugs in the regimen continued to give out. While this certainly suggests that Viread packs some hefty and long-lived antiviral activity, the data are still too mysterious to say this for certain.

Other key Viread studies include GS 907, a larger (Phase III) version of GS 902 in which 552 HIV-positive patients who are failing their most recent antiretroviral drug regimen are being randomized to intensify their treatment with either Viread or placebo. Forty-eight-week data from this study will be presented at the 41st ICAAC meeting in Chicago, to be held in late September.

If you currently face limited treatment options and require Viread to help control your viral load, your best bet might be through an expanded access program set up by the company. In this program, drug is provided for free – no risk of placebo here – in exchange for regular blood tests to help the company further prove the drug’s safety and effectiveness. To learn more about the expanded access program for Viread, your doctor can call the company directly: 1-877-226-8802 or 1-800-445-3235.

Also being conducted is GS 903, a study of Viread in combination with efavirenz (Sustiva), 3TC, and d4T in patients starting therapy for the first time. Preliminary results from this study are expected early next year, probably around the time the drug makes its way onto pharmacy shelves.



CRIA

is pleased to announce the publication of our first Spanish-language brochure:

Entendiendo Sus Resultados del Laboratorio

(Understanding Your Lab Results)

This brochure provides an easy to understand explanation of the different lab tests used to monitor the health of people living with HIV.

All of CRIA’s brochures, including

Clinical Trials Explained
Managing Drug Side Effects
Understanding Your Lab Results

are available free to AIDS service organizations and people with HIV/AIDS.

To order, contact Judy Codrington at (212) 924-3934 x121, write:

CRIA, 230 W. 38th Street,
17th floor, NY, NY 10018

or email: treatmented@criany.org

Just the FAQs *(continued from page 4)*

are causing drug resistance and drug failure. Phenotypic testing is a more direct measure of resistance and, more specifically, the actual sensitivity of your HIV to individual anti-retrovirals.

What is genotypic testing?

- Genotypic resistance testing examines the actual structure – or genotype – of your HIV (a standard blood sample is all that’s required). The HIV is examined for the presence of specific mutations that are known to cause resistance to certain drugs.
- For example, we know that Epivir isn’t effective against HIV that contains the M184V mutation in its reverse transcriptase enzyme. If a genotypic test discovers this mutation, chances are that your HIV is resistant to Epivir and won’t respond to the drug.
- Many drugs, including the protease inhibitors, require complex patterns of mutations for resistance to occur.
- With a genotypic test, the genetic sequences of particular viral enzymes – such as reverse transcriptase and protease – are examined carefully for mutations. Depending on the type and number of mutations found, the lab can determine whether someone has developed resistance to a specific drug, since almost all drugs follow a set pattern of mutations.
- There are actually two types of genotypic tests: sequencing assays and point-mutation assays. Sequencing assays look for any mutation in either the reverse transcriptase or protease enzymes. Point-mutation assays look for key mutations in these enzymes that are known to cause drug resistance. Most labs use point-mutation assays, as they are easier (and cheaper) to perform and their results are easier to interpret.
- For genotypic tests to be accurate, they generally require a blood sample from someone who is currently on therapy and has a viral load higher than 1,000 copies/mL.
- If you stop therapy before blood is drawn, the wild-type virus in your body may outgrow the mutant virus. This would result in the genotypic test “reading” the wild-type strain, which wouldn’t show any signs of resistance. In other words, it’s important that you’re still taking your drugs at the time of genotypic testing.
- Genotypic testing can take as little as a few days to complete, and a single genotypic test costs between \$300 and \$500. Many public and private health insurance programs cover the cost.

How are genotypic test results reported?

- When genotypic testing results come back from the lab, they list the mutations that were found in the virus’ reverse transcriptase and protease enzymes. It’s important to understand how these mutations are reported.
- An example: The M184V mutation is responsible for causing resistance to Epivir. The 184 refers to the amino acid position, or codon, in the reverse transcriptase enzyme. The M (methionine) is the amino acid at position 184 of a wild-type virus’

reverse transcriptase enzyme. The V (valine) refers to the mutation that results in drug resistance. In other words, the amino acid methionine at position 184 has been replaced by a valine, which prevents Epivir from binding with the enzyme to keep the virus from reproducing.

- While researchers have identified a number of mutations that can cause drug resistance, they don’t know everything there is to know about these mutations. We know that some combinations of mutations cause HIV to become more resistant than other combinations of mutations. Researchers are still trying to determine which sequences of mutations are the most important.
- Some genetic mutations have yet to be fully identified. This is the case with Videx (ddI) and Zerit (d4T). Resistance certainly occurs with these drugs, but researchers are only beginning to determine which mutations cause HIV to become less sensitive to them.
- Mutations known to cause resistance to Retrovir (AZT) and Epivir can also be misleading. A genotypic test may show that your HIV has several mutations that cause resistance to AZT. However, if you’re also taking Epivir – which seems to increase HIV’s sensitivity to AZT – these mutations may not accurately reflect the degree of AZT resistance.
- Another limitation: genotypic tests don’t evaluate the genetic structure of small HIV populations found in a blood sample. Unless a particular strain accounts for more than 20% of the HIV in a sample, chances are that it won’t be recognized by the test.

What is phenotypic testing?

- Unlike genotypic testing, which looks for particular genetic mutations that cause drug resistance, phenotypic testing directly measures the sensitivity – or phenotype – of your HIV in response to particular antiviral drugs.
- Phenotypic resistance tests measure the concentration of a drug required to inhibit viral replication in the test tube by a defined amount such as 50% or 95%. This is called IC50 or IC95 (IC stands for inhibitory concentration). If it only takes a standard amount of the drug to stop HIV from reproducing – a concentration equal to the usual dose – HIV isn’t resistant to the drug. If higher amounts of the drug are needed, HIV is considered to be resistant to that drug.
- The concentration of drug necessary to inhibit virus replication is expressed in nanomoles (nM). For example, if 100nM of a particular drug is needed to suppress wild-type HIV, but it takes 400nM to suppress virus found in your blood sample, your HIV is said to be fourfold resistant to the drug being tested. In other words, your HIV is four times less sensitive to the drug.
- Unlike genotypic tests, phenotypic tests generally don’t require a high viral load. Like genotypic tests, however, it is recommended that you be taking therapy when blood is drawn for phenotyping.

- Because phenotypic testing directly measures the sensitivity of HIV to particular drugs, many researchers believe that these tests are more comprehensive and trustworthy than genotypic tests.
- Phenotypic testing procedures are relatively complex and can take longer than genotypic tests to produce accurate results – from ten days to several weeks. They’re also more expensive. A single phenotypic test can cost between \$700 and \$900. Not all public and private health insurance programs cover phenotypic testing – be sure to check with your healthcare provider before having the test done.
- Phenotypic tests can’t evaluate the sensitivity of small HIV populations found in a blood sample. Unless a particular strain accounts for more than 10% to 20% of the HIV population in the sample, chances are that it won’t be recognized.
- Another challenge is that we still don’t fully understand what level of resistance translates into treatment failure. For example, a five-, six-, or sevenfold reduction in the sensitivity of HIV to a protease inhibitor is considered "moderate." But is there a significant difference between a fivefold reduction and a sevenfold reduction? Researchers are still trying to figure out what level of resistance means that a drug is no longer useful.

Can drug-resistance tests be used before you first start therapy?

- Maybe. Based on what is known about HIV's error-prone reproduction process, it's safe to assume that everyone has at least a few strains of virus that are resistant to individual drugs before therapy is started. However, these strains are often too limited in number and strength to compete with wild-type virus and stand a good chance of being killed off when you start therapy. In other words, genotypic or phenotypic testing might not provide an accurate picture of drug resistance before therapy is started.
- Drug-resistance tests might be useful for people infected with multiple-drug-resistant (MDR) strains of HIV. Soon after an MDR strain enters the body, it begins reproducing. Over time, a wild-type strain dominates the viral population. In order for resistance tests to be useful, blood will probably need to be drawn soon after infection takes place (within a few weeks). Only a small percentage of people know when they're infected or immediately see a healthcare provider.

Can drug-resistance tests be used to choose a new drug regimen after an initial one fails?

- Yes. Viral load tests can help determine whether or not drug failure is occurring, but resistance tests may play an invaluable role in helping you and your doctor understand why failure has occurred and what treatment options are still available.
- If viral load fails to become undetectable or becomes detectable again after being undetectable, resistance testing may help determine the cause. If no mutations are present (using genotypic assays) or the HIV is still sensitive to the

drugs you're taking (using phenotypic assays), the problem might be poor adherence or poor absorption. It's best to resolve these problems before resistance mutations develop.

- If mutations are found or HIV is determined to be losing sensitivity to the drugs being used, resistance tests can help determine which of the remaining antiretrovirals might be effective.
- Without resistance tests, it's recommended that anyone who appears to be failing a combination should switch to an entirely new batch of drugs. This can be frustrating, as many people don't have three or more untried drugs to choose from. It may also be a wasteful decision if your virus is still sensitive to some of the drugs you're currently taking. A number of studies conducted over the past few years have shown that, when viral load rebounds while on treatment, the virus is usually not resistant to all three (or more) drugs being used. So it's always good to know which drugs the virus has become resistant to and which drugs the virus remains sensitive to.
- Resistance tests may be able to help you and your doctor choose a new regimen after an initial regimen has failed, possibly helping to weed out the ineffective drug or drugs in a given combination.
- Resistance testing can also help determine what can be done about partial resistance. For example, a phenotypic test might determine that HIV is partially – as opposed to completely – resistant to a certain protease inhibitor (e.g., Crixivan). In this case, it might be possible to add a low dose of Norvir to increase the amount of Crixivan in the body. By increasing Crixivan levels, there's more drug available to combat the partially resistant virus.

How can drug resistance be avoided?

- **Learn as much as possible about anti-HIV drugs.** The more you know, the easier it will be to make treatment choices that can help avoid drug resistance.
- **Start treatment with a powerful anti-HIV regimen.** The first drug regimen you take may be your best chance to fully suppress the virus and prevent the development of drug resistance.
- **Follow instructions.** It's very important to take your medications exactly as prescribed. Missing doses, not taking the right number of pills, or eating when pills need to be taken on an empty stomach, can all cause viral load to increase and drug-resistance mutations to develop.
- **Good communication with a healthcare provider.** Asking questions and reporting any problems to your healthcare provider are important for avoiding drug resistance.
- **Regular viral load testing matters.** An increasing viral load is often the first sign that drug resistance is developing. Monitoring viral load regularly is a good way to guard against resistance.

Tim Horn is executive editor of the PRN Notebook, published by Physicians' Research Network in New York.

The Quality of Life of *CRIA Update* Readers: Survey Results

by Bruce D. Rapkin, Ph.D.

The Winter 2000/2001 issue of *CRIA Update* included several articles that explored the topic of quality of life. In preparing that issue, we saw an opportunity to share with *CRIA* readers the inner workings of this important area of clinical research. What better way to illustrate the advantages and limitations of different approaches to quality of life measurement than to conduct a survey of our readership? Readers received a one-page questionnaire that asked about their quality of life. We included a standard quantitative measure developed by Ware and colleagues (1994), the Medical Outcome Study 12 Item Short Form (SF-12), six qualitative or "idiographic" questions that my colleagues and I have used in our studies, and demographic questions.

We received responses from 118 people, including 48 by mail and 70 on-line. This response was more than sufficient for us to carry out statistical analyses. As is often the case in quality of life research, a number of surveys were returned with answers missing or incomplete. However, statistical methods allowed us to make adjustments for this missing data. Of course, this group of respondents represents a "self-selected sample." We have no way of knowing how well these responses represent the population of *CRIA Update* readers. Certainly, our sample, primarily composed of college-educated Caucasian men, does not reflect the current epidemic in the United States. Even so, the answers that we received were very informative about concerns that many readers may share. Respondents used the survey to express their hopes, struggles and disappointments. The editors of *CRIA Update* and I want to convey our gratitude to the people who took the time and effort to respond to this survey. We hope that you will enjoy learning how your answers contributed to the overall picture, portrayed in the results that follow.

Respondent Characteristics

Among those who answered this survey, 76% were male, 76% were Caucasian,

10% were people of African descent, 7% described themselves as Hispanic, and 6% were of mixed or other descent. The age of respondents spanned from 18 to 89 years, but over half the sample fell in a much narrower range, from 37 to 51 years. The sample reported high level of formal education, with 22% completing a graduate degree, 26% a bachelors degree, and 39% some college. Respondents encompassed a wide range of occupations, including management (19%), office or sales work (18%), counseling and teaching (15%), manual or service work (15%), high technology (13%), the arts (11%), and health care (8%). In terms of serostatus, 86% of respondents reported that they had tested positive for HIV. Years since HIV diagnosis ranged from 1 to 21, with a median (middle score) of about 8 1/2 years. Many in the sample were currently involved in one or more HIV-related activities, including volunteers (39%), activists (37%), donors (31%), and care givers (25%). Professional providers made up 16% of the sample, while 12% were HIV researchers.

Responses to Quantitative Items

Table 1 summarizes responses to the SF-12 items. Results for HIV positive and HIV negative respondents are presented

separately. The majority of people in each group described their health as good to excellent. Despite this overall positive rating, many people describe some physical limitations or difficulties at least some of the time. Emotional problems were somewhat more common than physical. In most instances, seropositive individuals reported greater health problems or limitations compared to seronegatives, especially in terms of ratings of general health, physical limits on accomplishments, being distracted by emotions at work, interference from pain, and disrupted social activities. However, there were also considerable areas of overlap between these two groups. For example, both groups described limitations in doing moderate activities and climbing stairs. HIV positive respondents reported feeling calm and peaceful more than those who were HIV negative.

In order to gain additional insight into quality of life differences among respondents to our survey, we examined the statistical correlation among each of the demographic variables and the SF-12 items. A perfect positive correlation of 1.00 between two variables means that as one variable goes up or down so does the other. A perfect negative correlation of -1.00 means that variables are opposite:

Table 1: Responses to the SF-12 Quality of Life Measure

PROPORTION OF RESPONDENTS WHO REPORTED:	HIV+ (100)	HIV- (17)
Good to Excellent Health *	71%	94%
Any Limitations with Moderate Activities (like vacuuming)	37%	25%
Any Limitations Climbing Stairs	46%	47%
Accomplishing Less due to Health, at least some of the time *	55%	24%
Health Limitation in Work or Activities, at least some of the time	51%	27%
Accomplishing Less due to Emotions, at least some of the time	62%	41%
Being Less Careful at Work, at least some of the time *	56%	27%
Interference from Pain, at least moderately *	32%	13%
Feeling Calm and Peaceful, most or all of the time	24%	17%
Having Lots of Energy, most or all of the time	26%	42%
Feeling Downhearted and Depressed, at least some of the time	67%	68%
Interference with Social Activities, at least some of the time *	56%	26%

* Differences between HIV+ & HIV- were statistically significant on these items.

as one goes up the other always goes down. A zero correlation means that differences in one variable are unrelated to difference in the other.

Our analysis showed several interesting patterns of correlations between quality of life items and respondent characteristics. For example, compared to women, men reported greater depression (.30), less calm (-.25), more interference with activities (.20), and greater difficulty accomplishing tasks (.23). Compared to Caucasian respondents, ethnic minorities reported worse overall health (-.32), more limits in moderate activities (.29) and climbing stairs (.30), and greater difficulty accomplishing tasks (.20). Among the different occupations, people in management positions expressed the least positive quality of life, in terms of limitations at work (.36), more limits in moderate activities (.25) and greater feelings of depression (.28).

Responses to Qualitative Items

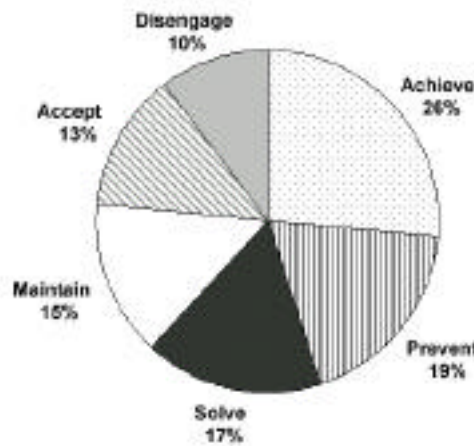
Although these quantitative results show differences among people, they do not tell us why those differences occur. Qualitative items can help us to gain a better understanding of what quality of life means to different individuals. In this survey, we asked people to describe the personal goals that mattered most to their quality of life. People responded to six different probes:

- (A) What things did they want to accomplish? (Achievement)
- (B) What situations did they want to prevent or avoid? (Avoidance)
- (C) What problems did they want to solve? (Problem Solving)
- (D) What things did they want to keep as they are? (Maintenance)
- (E) What circumstances are they trying to accept? (Acceptance)
- (F) What responsibilities or roles did they want to let go? (Disengagement)

On average, respondents mentioned 8.6 goals, with a range from 1 to 30 statements. Note that mail-in respondents were limited to mentioning up to 6 goals,

and almost all did. On-line respondents could write in additional responses. The average number of goals reported on-line was 11.13, almost twice as many as by mail. In order to account for this difference in the analysis discussed below, we summarized answers so that each person counted once no matter how many goals he or she mentioned. Figure 1 summarizes the proportion of goals given to each of the six probes. People mentioned more achievement goals than disengagement and acceptance goals combined, with responses to other questions intermediate, as shown by the size of the pie slices.

Figure 1: Responses to Goal Probes



In order to work with qualitative data, researchers sometimes develop codes to indicate properties of different responses. For example, the goal, “I want to help my family come to terms with my serostatus” includes themes of *family*, *supporting others*, and *HIV-specific*. The goal, “I want to make peace with the realization that some members of my family will never come to terms with my serostatus” includes themes of *family*, *HIV-specific*, and *psychological status*. By coding goal statements in this way, it is possible to boil down many individual statements into a set of common themes and concerns.

Figure 2 (next page) depicts themes and concerns mentioned by HIV+ and HIV- respondents. The most prevalent concerns mentioned by people living with HIV include psychological status and health

and illness. Other prevalent themes were work and school roles, practical tasks and financial concerns, travel, and relationships. Across all other themes, about 1 in 4 of the goals mentioned by people living with the virus involved HIV-specific concerns. Seronegative respondents also tended to express concerns about psychological status, roles, and practical demands, but offered fewer goals pertaining to health or to the health care system. Instead, these respondents mentioned relatively more goals pertaining to relationships. About 1 in 20 of the HIV negative respondents’ goals involved HIV in any way.

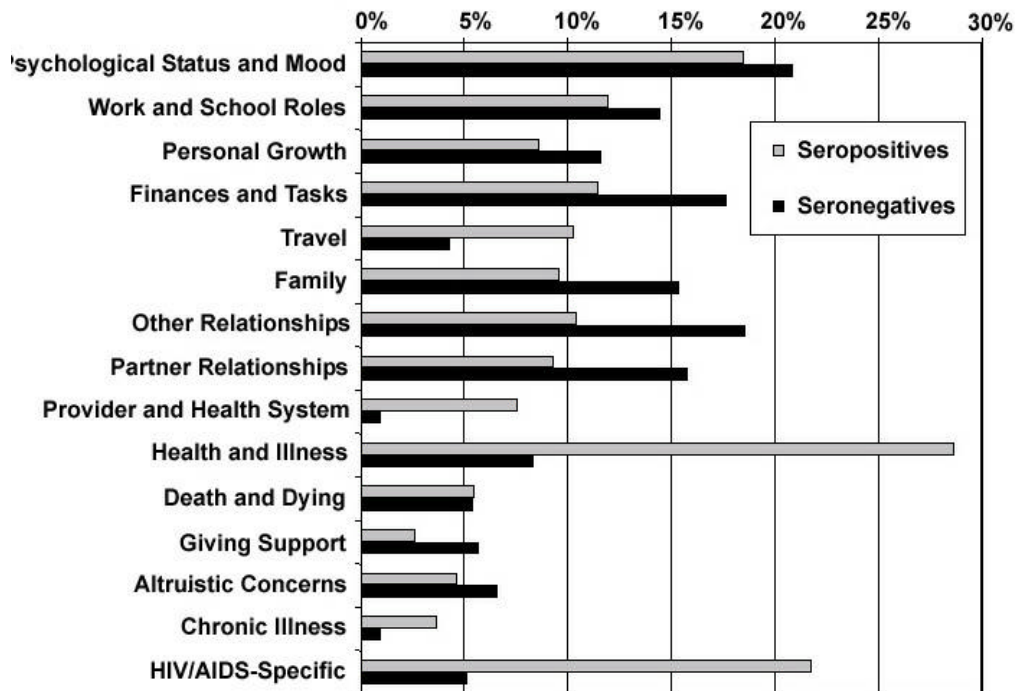
Integrating and Interpreting Quality of Life Data

Our quantitative findings showed that three subgroups in this sample expressed relatively diminished quality of life: men, minorities and managers. In order to gain some insight into the reasons why these groups seem to be faring worse than their counterparts, we used correlation analyses to examine differences in the personal goals. For example, the quality of life finding for males in this sample may reflect gender role differences in ways of coping with relationships. Compared to women, men wrote less frequently about providing support to others (-.24), accepting limits or difficulties in family and friend relationships (-.22) or community activities (-.26), and disengaging from supportive roles (-.30) and efforts at personal growth (-.25). In sum, men seemed to be less involved with others, and also less concerned with making choices about the quality of relationships: what to live with and what to let go.

Different factors were associated with the quality of life of minority respondents. Compared to Anglo-Caucasians, minorities were more involved with goals related to the health care system and treatment (.23). They also reported more efforts to disengage from providers (.24) and from dealing with health problems at all (.25). It is possible that difficulties obtaining support and care contributed to diminished sources of satisfaction in other areas. For instance, minority respondents

(continued on next page)

Figure 2: Proportion of Respondents Whose Goals Included Specific Themes



(continued from page 13)

were less involved with solving problems related to daily demands (-.25), perhaps because they were more focused on health-related problems. They were also less likely to be involved with maintaining friendships (-.21) but were more likely to report giving up personal growth related activities (.24).

Current or former managers also reported diminished quality of life compared to respondents with other occupations. More than other groups, managers reported more goals concerning health improvement (.23), addressing health problems other than HIV (.28), solving problems related to illness (.26) and providers (.31), and accepting health limitations. People in management jobs were also highly concerned with preventing problems associated with friendships (.26) and community activities (.24). This pattern suggests that people experienced in management roles are more heavily involved in trying to accomplish changes in their health and health care while protecting valued community and social roles. Perhaps the strain of trying to balance so much has taken a toll on the quality of life of these respondents.

Summary

It should be apparent that we have only begun to scratch the surface in terms of the richness and complexity involved in understanding quality of life. We hope that we have demonstrated how quality of life research can help to highlight the needs and concerns of specific groups. In the ideal case, findings such as those reported here would provide a basis for action for individuals as well as for concerned providers and activists. Research can serve to clarify priorities and point to resources needed to accomplish goals and improve quality of life.

Bruce D. Rapkin, Ph.D. is an associate professor of psychology in the Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center. Dr. Rapkin is the principal investigator on several studies of access to care and quality of life among people living with HIV/AIDS and their families.

Special thanks to Chloe Trouteur for generously volunteering her time to enter the survey results into our database, and to The Body for posting the survey on their website.

Community Forums

CRIA co-sponsors monthly educational forums on AIDS research and treatment issues.

Wednesday, October 17th
**The Kitchen Sink and More:
 New Antivirals
 & Evolving Strategies**

Wednesday, November 14th
**Body Shape Changes:
 Weight Loss & Fat
 Redistribution**

Wednesday, December 19th
Rectal Health

Forums are held at 7pm in the Cronin Auditorium, 10th floor of St. Vincent's Hospital at 12th St. and 7th Ave., Manhattan. Summaries of past forums are available on CRIA's website: www.criany.org.

Special thanks to:

HIV InSite

at the University of California, San Francisco for their assistance in identifying trial sites and gathering data for CRIA's HIV/AIDS clinical trials directory.

Visit their website at:

hivinsite.uscf.edu

for extensive information on HIV/AIDS clinical trials and treatment.

CRIA Welcomes New Staff Member

CRIA is pleased to introduce Eugen Vartolomie, MD as our newest researcher. Dr. Vartolomie comes to us from Bronx-Lebanon Hospital Center where he conducted HIV and AIDS related research within its Infectious Diseases Clinic. He received his MD in his native country of Romania, where he also specialized in HIV research, principally surrounding CMV Retinitis.

At CRIA, Dr. Vartolomie is managing our various protocols within partner clinics and hospitals in Brooklyn and Staten Island. This is the first time that CRIA has been able to dedicate a researcher to conducting trials within these two outer boroughs of New York City. Having this additional capacity represents an important advancement in CRIA's ability to ensure that all populations within our local community can potentially benefit from our HIV clinical trials.

Complementary Therapies Study Initiated

In July 2001, CRIA launched a protocol in collaboration with Linda Richmond, Ph.D. at Village Center for Care to evaluate the acceptance, use, and benefits of complementary therapies for people who are living with HIV. Dr. Richmond will be interviewing care providers and patients at several day treatment centers in New York City to learn which complementary therapies are most popular and seemingly effective. We will be examining such modalities as herbal therapy, meditation, reflexology, Reiki, and yoga through this process.

This study is being conducted as a preliminary step before designing a series of independent trials on the most promising of the "alternative" medicines. Our ultimate goal is to offer PLWAs and care providers more safety and efficacy data on these modalities than is currently available. We expect to have the explanatory model of complementary therapies completed by the end of 2001.

CRIA Begins Studying New Protease Inhibitor Atazanavir

CRIA will soon begin a Phase III double-blinded trial of Bristol-Myers Squibb's new protease inhibitor, atazanavir (formerly known as BMS-232632). The study's purpose will be to gather safety and efficacy information on this antiretroviral agent, which has yet to receive FDA approval. We will be primarily comparing atazanavir to nelfinavir (Viracept), a widely used protease inhibitor already on the market. Our objective will be to see which if either of these two medications is safer and/or more effective in fighting HIV. Trial participants will be randomized to receive either atazanavir plus two nucleoside reverse transcriptase inhibitors or nelfinavir plus two nucleoside reverse transcriptase inhibitors and will be followed through 11 site visits to CRIA's clinic over at least a 48-week period. People whose current regimen is failing them and who have never taken more than 7 days of protease inhibitor therapy are eligible to participate in the study.



is looking for new COMMUNITY ADVISORY BOARD members.

CRIA's Community Advisory Board (CAB) fosters partnership between the education staff and the local community impacted by HIV/AIDS. Involving community members in the development of our education programs ensures that community values and cultural differences are respected in CRIA's educational work.

Community Advisory Board members meet every other month, review program materials and help us identify education needs.

For more information about the CAB or if you are interested in volunteering at CRIA, please call Jen Curry at (212) 924-3934, ext. 120.

acknowledging our friends...

GENEROUS CONTRIBUTORS

The following persons, corporations and organizations made major donations between June 16, 2001 and September 14, 2001 to support CRIA's research and education efforts:

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The David Geffen Foundation
Agnes Gund and Daniel Shapiro
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Vanessa von Bismarck

Thoughtful donations in memory of the following remind us of what is at stake in the fight against AIDS:

Virgel Barraud
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James Learned
Rick A. Schwerte

COMMUNITY RESEARCH INITIATIVE ON AIDS

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