Once Upon A Time...

An evil virus clobbered all of the king's meds (and other fairy tales)

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The message about resistance has, from the start, read like a movie-thriller tagline: "Be afraid, be very afraid." The mutation monster from the antiretroviral lagoon -- it defies drugs, it turns the clock back to pre-HAART days, and it locks its teeth into everyone, even well-to-do, highly educated, intensely support-systemed HIVers getting cutting-edge medical care. In short: The Supervirus has arrived, so run for the hills.

The creepy music swelled again last December, when University of California at San Diego virologist Douglas Richman presented findings that nearly half of all current or former HAART-takers had resistance to at least one antiretroviral. The press latched onto the study, but its flurry of "AIDS Peril" stories failed to ask or answer the logical followup question: What the hell is the point, then? Why endure the endless pills, the blood tests, the tedious preoccupation with high-fat meals and better bowel movements?

Because the full story is neither so simple nor so black. Yes, viral resistance is a fact of life, but it's no reason to flush your meds down the toilet. In fact, how you deal with resistance -- and not only in the old "how well you adhere" sense -- can have a huge impact on how bad it can get.

Many docs are very hopeful that new treatment strategies can help keep pace with the virus' latest tricks. Simpler regimens have already offered welcome news to weary pill-poppers, as has delaying initial treatment. "Before it was hard. You crossed your fingers and hoped for the best," says Jason Leider, MD, director of adult HIV services for the North Bronx Health Care Network. "What's changed is drugs with forgiveness: long half-lives and low pill burdens."

Docs have also begun to notice that resistance is not an all-or-nothing proposition. Despite the doomsday ring of "treatment failure," drug resistance actually happens on a sliding scale, from "more effective" to "less effective." Even at the bottom end, there are still options for lifesaving treatment. As Howard Grossman, MD, a New York City AIDS doctor, explains, "I have some patients who, when they get their resistance tests, have all black boxes -- they're resistant to every single drug. But then you have to look closer: With which ones could you take steps to overcome *some* resistance?"

Best of all, far from being a mutant monster, there are indications that resistant HIV may be a Caspar Milquetoast that does a poor job of making you sick. All of this leaves many clinicians

surprisingly hopeful. “I feel like we’re in a new era, compared with four years ago when we only had nonboosted protease-inhibitor regimens,” says Harvard Medical School HIV doctor Valerie Stone, MD, an adherence specialist. “People have to realize that research is several years behind clinical practice.”

So what’s the best approach to besting resistance? Ask 10 experts, and you’ll get 10 answers. Treating drug-resistant virus is a Wild West affair, with few rules and lots of blowing smoke. But interviews with a dozen seasoned doctors -- from sources as diverse as a public hospital in the Bronx, an elite research institution, and one of the oldest private HIV practices in the country -- revealed one basic truth: You can do a lot to keep the resistance beast under control.

WHAT IS RESISTANCE, ANYWAY? HIV, like other viruses, spends most of its time and energy copying itself, and antiretroviral drugs physically interfere with that process. They work like a big hunk of steel shoved into a machine on an assembly line: When one goes down, the whole viral factory grinds to a halt. Three-drug combinations work better because they create three separate assembly-line breakdowns. As a result, most people starting on HAART see their viral loads plummet -- often to undetectable -- in just a few weeks. With the production line crippled, not much new virus gets produced.

Not much. That’s the problem. Even with triple-drug therapy, the virus still squeaks out enough versions of itself to protect its turf. Worse, a lot of those copies are random genetic mutants, each slightly different from the original “wild type.” By sheer chance, some of those mutants will be genetically different enough to get around the drugs: So while the three-drug combo has shut down some machines on the assembly line, the virus factory is getting back in motion without them.

Unfortunately, HIV usually accomplishes that pretty fast. A study of 358 treatment newbies by University of Alabama at Birmingham’s Michael Saag, MD, showed that on average, their first cocktail combo lasted only a year and a half before the virus resurfaced, and subsequent regimens failed even more quickly.

But resistance is not a black-and-white affair. Mutant viruses are more or less vulnerable to different drugs, and resistance tends to set in slowly and then gradually get worse as the virus evolves. Some mutations are better than others at circumventing drugs, and it often takes several different mutations for the drug to become virtually useless. The worst mutations can conquer whole classes of drugs at a time; this is called “cross-resistance.” (Non-nucleoside reverse transcriptase inhibitors, or NNRTIs, are especially vulnerable.)

Once the factory’s back on line, it resumes the mass production of HIV. Pretty soon your viral load creeps up, and your doctor declares you a “treatment failure” -- although, really, it’s the treatment that failed you. You switch to a new set of drugs, and with luck all is well for a year or so. But once your virus has outfoxed a drug, that drug will never again be as powerful as it was at first. With each trip on the cocktail merry-go-round, you lose options. Eventually, your viral load is back in the tens of thousands, your CD4s are faltering and your doctor starts talking about a seven-drug

“salvage” regimen. Not a movie you want to star in.

IF I’M NON-RESISTANT, HOW CAN I STAY THAT WAY? Most people who have never taken HIV meds -- the “treatment naïve” -- have wild-type virus sensitive to all HIV meds. But now, people are becoming infected from the get-go with virus that is already drug resistant. In fact, such folks make up 10 to 15 percent of all new cases of drug-resistant virus.

Delaying treatment: The days of testing positive and immediately starting meds are, for most HIVers, gone. If you haven’t yet gone on meds and your health is good, give waiting some serious thought. (And remember: It doesn’t have to mean you’re not doing anything for your health.) The federal guidelines were revised last year to discourage early intervention, leaving no hard-and-fast rules for people with CD4 counts above 200. If your CD4s are in the gray area between 200 and 350, factor future resistance into your decision. As it stands, you have a limited number of good drug options -- say, four rounds -- and you don’t yet know how long each will last. Saag’s study found that within two years of starting therapy, about one in five HIVers had changed combos three times. Delaying therapy may preserve more options.

Starting early: On the flip side, there’s plenty of evidence that replicating virus damages your immune system, destroying CD4s and other immune functions.

Testing for resistance: With drug-resistant virus on the loose, most docs agree that the treatment-naïve should get tested for resistance before you start HAART, even though official guidelines don’t recommend it (see “This Is Only a Test” below).

Taking your adherence pulse: Do a personal inventory about what you can handle -- taking drugs half-assedly is a recipe for resistance. Generally, doctors prescribe the simplest, most powerful cocktail first, and people do best on their first regimen. So don’t waste your best weapon by not being ready to commit.

Finding the right doc: What Douglas Richman, MD, found that didn’t make scary headlines was that resistance is lower among those treated by doctors with more than 100 HIV patients. This confirms common sense: A doctor must be able to analyze the results of viral load, CD4 and resistance tests, keep up with the torrent of new studies and intelligently choose from the cornucopia of combos and strategies. Inexperienced docs may not keep up. If you don’t have a crack doctor, contact the American Academy of HIV Medicine (310.278.6380, info@aahivm.org) or the HIV Medicine Association (703.299.1215, hivma@idsociety.org) for a list of local specialists.

Taking the long view: Beyond credentials, pick a doc you can talk honestly to, and who has your long-term health in mind, says Keith Henry, MD, director of HIV clinical research at Hennepin County Medical Center in Minneapolis: “It’s one thing to get the viral load low for the next visit, but the bigger question patients should ask is: Where is this going? What’s the five- and 10-year plan?”

WHICH DRUGS WILL HOLD OFF RESISTANCE THE LONGEST? Damn good question. Even the best in HIV medicine admit they don’t really know -- and many of the necessary studies just

haven’t been done.

Adhere, my dear: The one stone-cold fact is that compliance is crucial. Take your drugs exactly as prescribed and directed, and you’ll likely stave off resistance as long as possible. While many HIVers see viral breakthrough after only a year or so, says longtime Washington, DC, AIDS doc Bruce Rashbaum, MD, some of his patients have stayed on the same combo for six years or more. “The papers say cocktails fail after two or three years, but that is bunk,” he says. “If you take your drugs, they’re going to work.”

One 1999 study put this issue in a stark light: Of HIVers taking HAART for three months, 81 percent of those who were at least 95 percent adherent kept their virus at bay. (On a typical four-pills-twice-daily Combivir/Kaletra combo, that would mean they missed or mismanaged -- fudging the timing or food instructions -- less than three doses per month.) People who bungled just a couple more doses -- who were 90 to 95 percent adherent -- fared much worse. Only 64 percent kept their virus suppressed. The upshot is that missing just a few doses a month can help the virus stage a comeback.

The new once- or twice-a-day regimens go a long way toward making pill-popping easier. Harvard’s Valerie Stone says that HIVers shouldn’t be afraid to tell their doc, “I’d prefer a simpler regimen.”

You’re unique: So how come even anal-retentive, timer-beeper-pillbox types develop resistance? Because just like alcohol or coffee, drugs affect everybody differently. Your liver enzymes, for example, control how much of the pill gets into your blood in an active form. Drug levels are also influenced by your body size, genetics, the other drugs and herbs you take, and whether you’re a booze hound or have hepatitis B or C. Protease inhibitors are notoriously unpredictable in this way: One person may have 10 times as much PI in his or her blood as another on the same dose.

“My pet peeve is that patients often get blamed when the treatment fails,” says Jeffrey Greene, MD, another longtime New York City doctor. “The virus has the ability to develop resistance whether the patient is adherent or not. But the patient becomes the scapegoat for the pharmaceutical industry, which hasn’t done the proper tests [on drug metabolism].”

Testing drug levels: Therapeutic drug monitoring is a new technique that can measure how much drug actually gets into your blood, allowing your doctor to fine-tune your regimen for your metabolic quirks. It’s not used much in this country, but as the technology improves, it could help docs tweak cocktails to make them more powerful and longer lasting.

VIRAL LOAD HAS BROKEN THROUGH, AND MY TREATMENT IS FAILING. WHAT ARE MY OPTIONS? This is one of the toughest treatment decisions you’ll ever have to make, so keep your cool. First, get a second test to confirm that your viral load is truly breaking through rather than merely blipping (see “Blip Gloss” below). Second, remember that *treatment failure* is a stupid term. Few drugs fail overnight. Rather, they become a lot or a little less effective as your virus develops degrees of resistance.

When to switch is a hot debate. While federal guidelines recommend considering a new cocktail whenever previously undetectable virus climbs above 50 copies and stays there, every physician has his or her own approach to deciding how much virus is too much. “This is the most critical question,” says the North Bronx’s Leider. “If you’re too eager, you could burn through the good drugs. If you keep people on a failing regimen too long, they will build up further resistance” -- additional mutations that either erode a drug’s power more or create cross-resistance -- “and you again have no options.”

What really gets under the skin of some HIV docs is that they are partly to blame for the swelling tide of drug resistance. With few options, an imperfect understanding of how the drugs work and a fear of side effects, they have done a lot of quick combo switching that, in hindsight, looks like a very bad idea. “In the U.S., we’ve been learning mistake by mistake,” says Henry. “Many that have resistance have gathered it sequentially, as drugs have become available.” A lot of docs are now much less eager to switch combos when they see detectable virus or signs of side effects. “I’ve never been stringent with changing treatment because virus is not completely undetectable,” says New York City’s Greene. “We only achieve undetectable with 60 percent of treatment-naïve patients. Besides, drugs do a lot of good, even when virus is not completely suppressed.”

Switching: The question is: How fast? Traditional thinking says switching quickly prohibits full-throttle cross-resistance, nipping it in the bud by keeping viral levels low with the new cocktail.

But increasingly, physicians are redrawing the lines for people on their third or fourth combo, postponing the change on the theory that sticking with an imperfect treatment still preserves more options for the future. Stone usually doesn’t tinker with a cocktail until the virus is consistently above 5,000 copies. Greene worries more about viral loads that change more quickly than ones that are consistent: If someone has never had a viral load below 1,000, but it’s stable, he would likely leave the regimen alone. But someone who’s been undetectable for years whose viral load suddenly jumps into the thousands sets off alarms. “Each patient has their own benchmark,” he says.

Adding a drug: Another possibility at this stage is to add one more drug to your combo -- either to “boost” levels of those drugs in an effort to overcome the resistance or to increase the failing combo’s anti-HIV punch. The two drugs most commonly used as so-called PK (“pharmacokinetic”) boosters, delavirdine (Rescriptor) and ritonavir (Norvir), work to increase the amount of protease inhibitor in your bloodstream. As Grossman explains, “I may find, for example, that a patient’s virus is 20-fold resistant to indinavir (Crixivan) -- in other words, their virus is 20 times less sensitive to that drug than is wild-type virus. Well, it’s very possible that with ritonavir boosting, you can overcome that amount of resistance.” In some cases, a booster may allow you to go down to a once-a-day dose.

Likewise, “intensification” adds a fourth drug to the three you’re already on, in the hope that increasing the arsenal will stave off switching to a new regimen. Again, choose sides: Some docs say this tactic amounts to throwing good drugs after bad -- wasting a functional drug along with the failing regimen. Others think it may allow you to stay with a powerful regimen for longer. Just

as three drugs can hold off virus longer than two drugs, four could prove that much more effective.

Blip Gloss

Failure is a funny word, at least the way doctors use it. Virologic failure, for a conservative physician, means two successive viral loads between 50 and 500 copies three months apart. But short-term viral spikes apparently aren't cause for cussin'.

A series of studies have shown that "blips" -- a viral spike above 50 copies -- in people who had otherwise-undetectable virus aren't an early sign of failure. In most cases, blippers fare just as well as nonblippers, both in terms of T-cell survival and overall viral load. Research from the Aaron Diamond AIDS Research Center indicates that these brief upticks are common, found in perhaps one out of 10 viral load tests.

So if you've been downing your meds faithfully, your virus has been undetectable and you suddenly get a high viral load test, don't flip out. Repeat the test right away -- and with luck the blip will have blipped out.

-- KM

IF MY VIRUS IS RESISTANT TO EVERYTHING, WHY AM I STILL TAKING DRUGS? If you've been through three or four rounds of meds, you may feel like you're at the end of your hope. But "virologic failure" is not the same thing as failing health. "You look at someone now with two T cells and viral load of 200,000, and they do much better than the same person would have eight years ago," says Washington, DC, AIDS doc Douglas Ward, MD. While the drugs don't pack the wallop they once did, they still help keep HIV in check. What to do? Again, it depends on who you ask. If you have no obvious drug options left, there are three common salvage strategies: Take a "kitchen sink" regimen that combines six to nine drugs at a time; stop completely for a while; stay on the failing -- let's call them "partially succeeding" -- drugs while you wait for new drugs to be approved (or try recycling failing drugs from the past).

Kitchen sink: This is a desperate measure. While it may bring your viral load down, the side effects can be so intense that you may be unable stick to it for long. Henry says he took to calling a salvage study in his clinic the *Les Miserables* trial.

STI: If CD4s are high and side effects a big problem, one tactic is to briefly stop treatment, allow wild-type virus to resurface, then whack it back with a partially active drug combo. It's a temporary fix, and risky with low CD4s, because once you go back on the drugs, the mutant virus that's been lurking inside you will multiply again pretty quickly.

Partial success: When you've run out of new drugs to take, many docs will either keep you on a failing combo or put you back on drugs you had stopped because of side effects or growing resistance. The theory here is that partial viral suppression is better than nothing. Birmingham's Saag says that his benchmark for partial suppression is a combination that will reduce the viral load by threefold: "If a patient off therapy has a viral load of 100,000, and I can get the patient to 30,000 or less and sustain it, the likelihood of clinical progression is quite low." His method:

Looking at genotypic and phenotypic tests and treatment history, he makes a list of which drugs are likely to have some limited effect. Then the patient chooses a cocktail, based on his or her prior experience with side effects and adherence success with each drug candidate.

On the bright side, new research by University of California at San Francisco's Steven Deeks, MD, has shown that a combination of partially effective drugs seems to hold off disease progression, even at relatively high viral loads (see "Failure is Sweet"). Exactly why is less clear. His theory rests on the idea of "viral fitness" -- that the viral mutants that have evolved to outsmart drugs simply aren't as effective at replicating and making you sick. For example, in the lab, PI-resistant HIV is much less able to reproduce itself than wild type -- a sign that it may not be so good at wandering around your body and wreaking havoc. If you have to choose between weak, mutated virus and strong, wild-type virus, goes the thinking, pick the less powerful, drug-resistant enemy.

More meds: For those in the salvage scenario, the best hope is, of course, new drugs, and there are a few promising ones on the horizon. The recently approved Viread has already shown success in HIVers who have failed classic regimens. And T-20, one of a new class of "entry inhibitors" that prevent HIV from attaching to cells, has shown good results in people with high-level resistance, working against the virus in a new way. Hoffman La-Roche plans to apply for approval this fall and has pledged to make it available for people with advanced HIV through expanded access. The downside: It requires twice-daily injections.

Another compound, the new non-nuke TMC 125, may play a role for people who have burned through the other NNRTIs. The Phase II trial of efficacy began enrollment last spring. A new protease inhibitor, tipranavir, may work against virus that's resistant to other PIs. That drug is in early trials but may be available through expanded access this October.

One last bright spot for all HIVers, whether drug resistant or not: More new formulations of old standbys will make pill-popping easier. Videx (ddI), Sustiva (efavirenz) and Viread (tenofovir) are all once-a-day doses, and Epivir (3TC) and Kaletra (lopinavir/ritonivir) are being looked at as workable once-dailies. It may seem trivial, but simpler cocktails are a potent weapon against resistance.

The funny thing is that just as we've gotten used to the mantra that resistance is inevitable, doctors are starting to seize or settle on ways to keep it in check. With any luck, the next few years' grim reports about resistance will be accompanied by headlines from studies that prove what front-line doctors already suspect: that the fight with HIV-resistant virus can be won.

THIS IS ONLY A TEST

Resistance tests, the newest tools in the HIV kit, can be helpful in choosing from the cocktail menu. The tests come in two flavors: genotypic and phenotypic. Neither will tell you which drug is best -- only which drugs probably won't work.

Genotypic tests do a genetic analysis of your virus to figure out what mutations it has developed. They're faster (results in a week or two) and cheaper ($400 to $600). Phenotypic tests pit your

virus directly against HIV meds in a test tube. Results are measured on a sliding scale of “sensitivity,” where high drug sensitivity generally means the drug will work in your body, and low equals resistance. They’re more expensive ($900 to $1,000) and slower (results take two to four weeks).

Each test gives you different information, and each doc has a preference (usually based on which he or she least misunderstands!). Generally your doctor will run a genotype before you begin treatment to check for possible resistance, adding or switching to phenotypic testing for second- or third-round decisions. Many docs use both following your first treatment failure, in order to get the clearest possible picture of what’s going on.

Two cautions: Neither works well if your viral load is below 50, and neither will be accurate if you’ve been drug-free for a while -- maybe even for a few weeks.

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