

The amfAR Treatment Insider

Table of Contents

- 1 Doctors Hesitate on Kaletra
- 3 Efavirenz role in salvage therapy.
- 5 Long-Term Strategy Trials

Doctors Hesitate On Kaletra

by Dave Gilden

On September 15, the FDA announced approval of a new HIV drug, Abbott Laboratories' new protease inhibitor formulation, Kaletra. Providentially for Abbott's marketing department, the agency's announcement came the eve of one of the largest biomedical conferences of the year (the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, or ICAAC). But Abbott's promotional drive has hit a snag as doctors, already burnt by drug-resistance and side-effect problems with other protease inhibitors, wonder when to prescribe this new entry in the antiretroviral drug sweepstakes.

Kaletra capsules contain a combination of 133 mg of the new protease inhibitor lopinavir (formerly known as ABT-378) plus 33 mg of Abbott's old protease inhibitor ritonavir. Normally, three capsules are taken twice a day.

One of ritonavir's side effects is to inhibit the breakdown of drugs by liver enzymes. This is its sole function in the Kaletra combination, since the dose of ritonavir is too low to have much of an anti-HIV effect. Kaletra, then, follows in the tradition of other "ritonavir-enhanced" protease inhibitor combinations. The first of these was ritonavir/saquinavir, both taken twice daily at a dose of 400 mg. Four years ago, the introduction of this combination made saquinavir a viable drug despite its very rapid elimination in the liver.

Adding ritonavir to lopinavir transforms it into a twice-a-day drug, whereas lopinavir ordinarily would start to disappear in about four hours. Abbott says that the added ritonavir in the twice-daily regimen also leads to 50 times higher, stable plasma levels of lopinavir, levels that are 75-fold higher than that needed to suppress normal, "wild-type" HIV by 50% (the EC₅₀ level). At those levels, lopinavir would be able to suppress HIV that contains mutations conferring significant resistance to the drug.

Such claims, based on laboratory tests of lopinavir's effectiveness, are immediately challenged by Hoffmann-La Roche, the maker of saquinavir and Abbott's competitor. Dr. Andrew Hill, Roche's Britain-based International Medical Manager for Fortovase, has argued at two recent scientific meetings that Abbott's figures are heavily distorted. He said, "There is no definitive data that any of the ritonavir-boosted PIs is better than another. In viral load, there is a standard way of testing. For *in vitro* efficacy, there may never be the standard, and a variety of estimates will exist."

One major issue is that most of the protease inhibitor in the body is bound to blood proteins and is unavailable to cells. The exact proportion varies from 60% to over 99%, depending on the drug, and this effect may not be taken into account in lab tests performed on HIV-infected cell cultures. Roche has now started an initiative to get drug companies to standardize the lab assays that gauge drug effectiveness. Uniform testing would allow better comparisons between drugs.

Kaletra in Salvage Therapy

The ultimate test is how well the various regimens perform in humans, and the data from clinical trials are very positive for Kaletra. In persons without prior treatment, a 653-person Phase III trial compared d4T / 3TC / Kaletra to d4T/3TC/nelfinavir (Viracept). At 40 weeks, 70% of those starting in the Kaletra arm had viral loads under 50 copies/mL whereas 54% in the nelfinavir arm did so.¹ (These figures come from an intent-to-treat analysis that counted as treatment failures those who altered their initial therapy.)

The results were almost as favorable in volunteers whose treatment histories included multiple protease inhibitors. One Kaletra salvage therapy trial enrolled 57 such persons with current viral loads over 1,000 copies/mL. (The trial participants had to have a history of more than three months on at least two different protease inhibitors and yet still be naïve to NNRTIs such as efavirenz (Sustiva). They received efavirenz and Kaletra plus two individually selected nucleoside analogs. All started on a Kaletra dosage of three capsules twice daily (400 mg lopinavir/100 mg ritonavir). After the first two weeks, half added an extra Kaletra capsule (for a total twice-daily dosage of 533 mg lopinavir and 133 mg ritonavir). At the end of 24 weeks, 82% of the people on this higher dose had viral loads below 400 copies/mL, compared to 69% of those on the lower dose. (These data were arrived at through the same sort of intent-to-treat analysis as the one above.)

In this trial, 68% of the volunteers had HIV with cross-resistance to three or more protease inhibitors. The results are taken to show that Kaletra is highly effective drug even in situations where protease inhibitor resistance abounds. On the other hand, the use of efavirenz in these NNRTI-naïve volunteers clouds the issue. Perhaps much of the success was due to the two nucleoside analogs plus efavirenz?

Dr. Eugene Sun, director of antiviral research at Abbott Laboratories, has little patience with this line of reasoning. "We've shown that the response rate depends on the amount of lopinavir resistance, so our drug must be central," he commented last June following a contentious Kaletra presentation at the 4th International Workshop on HIV Drug Resistance.

This fall, Abbott also presented further data indicating that the response rate to Kaletra depended on the blood levels of lopinavir achieved relative to the lopinavir resistance present in individual trial participants.³ Still, the doubts about the

relative roles of efavirenz and Kaletra are hard to resolve because this trial had no comparison arm that did not receive Kaletra.

Resistance to Kaletra

Many doctors prefer starting therapy with an efavirenz-containing regimen, which is a known quantity, rather than tempt fate with Kaletra, which they regard as uncharted territory. Dr. Mike Para, an HIV researcher at Ohio State University Medical Center in Columbus, said "I prefer to use non-nukes [NNRTIs] in initial therapy because they require fewer pills and are better tolerated. I want to save Kaletra for PI failures and NNRTI failures who also have resistance mutations for nucleoside analogs. Kaletra would be good if you don't feel comfortable that the nukes work as well as they should [in a particular patient]."

Part of doctors' fear of Kaletra is a lack of data about the frequency of the development of Kaletra-resistant HIV and the genetics behind that resistance. For this reason, they tend to look at it as a last-ditch agent to use when other drugs have failed. "Kaletra is a potent drug, but I don't know what I can replace it with if a patient has viral rebound," said Dr. Howard Grossman, an HIV specialist in New York City.

There is little information about lopinavir-resistant HIV in humans. Abbott has documented the development of some sort of drug resistance in 20 Kaletra trial participants who experienced HIV rebound while on Kaletra. (This analysis did not include anyone from the large nelfinavir versus Kaletra trial in treatment-naïve adults.) Of these 20, 15 (including two treatment-naïve individuals) had HIV that acquired resistance mutations to two other drugs in the regimen – 3TC and nevirapine or efavirenz. This development was associated with poor compliance in seven persons and with a high number (six to nine) of baseline protease mutations in the other eight. The protease mutations conferred broad protease inhibitor cross-resistance, including to lopinavir, apparently.⁴

In just five persons was there any sign of evolving lopinavir resistance during therapy. Four of these five could be further analyzed. The loss of susceptibility to lopinavir was associated with continued or new resistance to indinavir, ritonavir, nelfinavir and, in two of the cases, amprenavir.

When looking at the total pool of 13 persons with either baseline or acquired resistance to lopinavir, Abbott

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HIV in humans. Abbott has documented the development of some sort of drug resistance in 20 Kaletra trial participants who experienced HIV rebound while on Kaletra. (This

(continued on page 4)

Competition From Efavirenz

by Dave Gilden

Adding to the uncertainty about Kaletra's contribution in salvage therapy that also includes an NNRTI like efavirenz is evidence that HIV mutations conferring resistance to nucleoside analogs at the same time make the virus more susceptible to NNRTIs like efavirenz (Sustiva). At the 4th International Workshop on HIV Drug Resistance last June, Richard Haubrich of the University of California San Diego reported on this phenomenon. He noted that in a cohort of 164 treatment-experienced patients, 26% had HIV "hypersensitive" to efavirenz, 21% to delavirdine and 18% to nevirapine.¹

Hypersensitivity was defined as a reduction of at least 60% in the amount of drug necessary to suppress half of a patient's HIV replication as compared to the amount needed to cut "wild type" HIV replication by half. When efavirenz formed part of a salvage therapy regimen, persons with efavirenz-hypersensitive HIV experienced an extra 0.5 log (32%) decrease in HIV levels over those whose HIV was not hypersensitive to this NNRTI. This advantage decreased over the ten months the patients were followed. The effect of the patients' regimens waned overall, and viral loads in the hypersensitive and non-hypersensitive groups converged.

Then there is the randomized, controlled trial ACTG 364, described last winter at the 7th Conference on Retroviruses and Opportunistic Infections.² This trial was conducted in people who had viral loads above 500 copies/mL and extensive treatment histories on nucleoside analogs but *no* prior protease inhibitors or NNRTIs. All received two nucleoside analogs plus either efavirenz, the protease inhibitor nelfinavir or both. The efavirenz and combination arms did significantly better than the nelfinavir arm, whose proportion with viral loads below 400 copies/mL rapidly dropped off after week 16. At week 40-48, the proportion below 400 was 35% for nelfinavir, 60% for efavirenz and 74% for efavirenz plus nelfinavir. (The proportions with viral loads below 50 copies/mL at week 40-48 were 22%, 44% and 67%, respectively.)

The efavirenz superiority in this trial might indicate merely that using a once-a-day drug like efavirenz with mild mental side effects may yield better patient adherence to dosing schedules than a three-times-a-day, chronic diarrhea-causing drug like nelfinavir. But the effect of nucleoside analogs in this cohort was no doubt limited. It is hard to imagine why efavirenz resistance would not quickly arise without strong support from these nucleoside analogs. An association of nucleoside analog resistance with hypersensitivity to efavirenz would help to explain ACTG 364's outcome.

Be that as it may, the indications are that hypersensitivity to efavirenz made at best a very limited contribution to the results: As in the San Diego study, the potency of efavirenz in salvage therapy in this trial diminished over time compared to the nelfinavir-efavirenz combination arm. At 16 weeks, the proportion below 50 copies/mL in the efavirenz arm peaked at about 58%. In the combination arm, the week 16 percentage was about 60% and continued to increase through week 32. Countering any suggestion of a long-term role for efavirenz hypersensitivity, predictors of viral load below 50 at week 48 included having HIV with less nucleoside analog resistance rather than more.

Note that although benefits obtained from efavirenz-based salvage regimens may be debatable, the results for initial therapy are much more impressive. For example, in trial 006 performed by efavirenz developer DuPont Pharmaceuticals, 68% of volunteers starting on an AZT/3TC/efavirenz regimen had viral loads below 50 copies/mL after one year. Fifty-nine percent still had this level of success after 112 weeks.³

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(continued from page 2)

could find no definite pattern here, either. Its researchers associated lopinavir resistance with a number of the standard HIV mutations that confer resistance to other protease inhibitors. The company analysis indicated that lopinavir failure was associated with the total number of mutations in the protease gene as well as with inability to include effective nucleoside analogs that would give lopinavir support in suppressing HIV replication. Based on an analysis of the persons in the multiple-PI failure trial, Abbott says the chance of lopinavir failure reaches 50% when the number of protease mutations is about six.⁵

Still, certain common single mutations (at protease amino acids 20, 53, 54 and 82) are particularly troubling for lopinavir. A combination of just two of them could confer a ten-fold or more loss in susceptibility to lopinavir. These mutations could also spell broad cross-resistance to succeeding protease inhibitors. In three people with lopinavir-resistant HIV, Abbott researchers did find some continuing viral sensitivity to amprenavir and saquinavir in lab assays. Protease inhibitor rescue after lopinavir failure may require a protease inhibitor of radically different design, such as Boehringer Ingelheim's tipranavir, which is still in Phase I testing.

Kaletra vs. Other Ritonavir-Enhanced PIs

In the past year, there has been a markedly increasing tendency for doctors to prescribe ritonavir-enhanced regimens that include indinavir, saquinavir or amprenavir. In the past, Abbott has tested and recommended regimens involving 400 mg of ritonavir and 400 mg of either indinavir or saquinavir. Merck and Roche, these latter two drugs' manufacturers, have lately tested reduced doses of ritonavir – 100 or 200 mg – with higher doses of their own drugs – 800 mg for indinavir and up to 1600 mg for saquinavir – in once- or twice-daily regimens. An ongoing French study is comparing a particularly low-dose, inexpensive combination that contains just 400 mg of indinavir and 100 mg of ritonavir taken twice-a-day. Other researchers have tested 100 mg of ritonavir twice daily in combination with 600 mg of Glaxo's protease inhibitor amprenavir.

In all cases, adding the ritonavir stabilizes the other PI in the body to the extent that total pill burdens are reduced as well as dosing schedules. In the case of indinavir/ritonavir, even Abbott agrees that trough levels of indinavir are raised to about 25 times the EC₅₀ for the 800/100 indinavir/ritonavir combination.⁶

Ritonavir itself has a host of side effects, including increased blood lipids, taste perversion, stomach upset and numbness around the lips and other areas. These

days, it is prescribed only occasionally as a single protease inhibitor at the full 600 mg dose. Lowering the traditional 400 mg dose used in ritonavir-enhanced PI regimens to only 100 or 200 mg further reduces ritonavir's toxicities. But Dr. Keith Henry, who heads the HIV salvage therapy clinic of Regions Hospital in St. Paul, MN noted, "People on ritonavir still have some problems with it, but the dose is lower than what they were on. For ritonavir virgins, even the low end is a jolt, but it's not as bad as what used to happen."

With the introduction of the 400 mg lopinavir/100 mg ritonavir combination, Abbott itself seems to have bought into the argument for ritonavir "minidosing." Still, Henry complains, "This is the first time that we've had ritonavir enhancement built in. So the data are cleaner as there is no need to establish intercompany cooperation. But I don't know how unique lopinavir plus ritonavir is. Comparison trials do not seem to be getting done."

Various trials have tested other ritonavir-enhanced regimens through the years. One recent such trial tried saquinavir/ritonavir at a twice-daily dose of 1000 mg/100 mg plus efavirenz and two nucleoside analogs in 32 persons.⁷ On enrollment, the volunteers were all failing their first protease inhibitor-containing regimen, with baseline viral loads over 5,000 copies/mL. They all also had never taken saquinavir or any NNRTI. At week 48, 56% had viral loads below 50 copies/mL. Last September, preliminary results from an indinavir/ritonavir salvage therapy trial were presented at the ICAAC.⁸ The 72 trial participants all had previously received indinavir and had "failed" at least one PI-containing regimen. In the trial, they received indinavir/ritonavir twice daily at doses of 800 mg /200 mg (47 volunteers) or 400 mg/400 mg (25 volunteers). They also received supporting nucleoside analogs and, in two-thirds of the cases, NNRTIs. At 12 weeks, 24 of the 44 volunteers (55%) on the 800/200 regimen with results available had viral loads under 400 copies/mL compared to 8 of 24 (33%) on the 400/400 combination.

This indinavir/ritonavir study has the merit of comparing different doses of the combination. Without any agreement on how much ritonavir or the other drugs to use, it is difficult to evaluate any of the results. It is also hard to run the head-to-head trials with Kaletra that doctors are calling for.

Hoffman-La Roche is proceeding with one 300-person, one-year trial comparing 1000 mg saquinavir/100 mg ritonavir, Roche's favorite version of the combination, to 800 mg indinavir/100 mg ritonavir, both twice daily, in treatment-naïve and -experienced volunteers. That trial, with 40 sites in Europe, South America and the United

States, is now enrolling. A similar trial testing the same saquinavir/ritonavir regimen against the standard Kaletra dose is in the planning stages.

Awaiting the Community's Experience

Abbott does have one cohort of treatment-naïve individuals who have taken Kaletra for two years. The cohort, which started with 100 volunteers and now numbers 86, has been remarkably stable. Nearly all (92%) of the remaining members have viral loads below 50 at week 96, making for a 78% success rate by intent-to-treat standards. Side effects have been low, with loose stools or diarrhea in a quarter of the group being the most common problem. High cholesterol levels occurred in 14 of the 100 and high blood triglycerides in 12.

Trial cohorts frequently do not reflect the population as a whole. Keith Henry worried, "It's just a matter of time to see Kaletra-specific side effects – we don't know what yet." Other doctors are convinced that they are already seeing increases in blood lipids tied to the lopinavir rather than the ritonavir. In the end, "we don't know yet" sums up the medical community's view of Kaletra. Four years ago, Abbott's ritonavir crashed in the real world as a stand-alone protease inhibitor despite impressive trial data. Patients found its gastric and other side effects intolerable. Further experience with Kaletra will decide this drug's ultimate popularity, too.

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In for the Long Haul: Debate Paves Way for Long-Term Trials

by Emily Bass

A small group of community advocates, a divided research community, huge sums of money, and urgent questions that threaten to break the mold of conventional trial designs. All of these elements are at play in what may be one of the least publicized and most critical fields in HIV research today: long-term trial design. The National Institute of Allergy and Infectious Diseases (NIAID) has earmarked approximately \$80 million dollars for studies to answer such crucial questions as when to start and when to change HIV therapy. Some trials, particularly large, international collaborations, could cost even more.

Taking on long-term management questions has, once again, brought HIV to the frontier of existing medical expertise. In January 2000, a NIAID Department of AIDS (DAIDS) meeting brought together researchers, clinicians, community advocates, statisticians and experts from cardiovascular and cancer research to discuss how best to answer long-term questions in the field of HIV disease management. The results were stimulating and daunting. "The word we got from people in cancer and heart disease was that this is at the cutting edge of clinical trials methodology in some ways," said DAIDS director Jack Killen. "There has been very little work in any field of clinical research that looks at very long-term outcomes over a very long period of time."

One of the major challenges is the sheer size of the trials. A study pool of many thousands of people is required to detect a meaningful reduction in the risk of "events" – i.e. death, severe toxicities or disease progression – associated with long-term use of particular treatment regimen or strategy. HIV treatment strategy trials of all kinds will, by necessity, enroll relatively healthy patients. It is medically and ethically indefensible not to treat those who are already sick or have CD4 counts below 200 cells/mm³. Starting with healthy individuals means it could be years before the effect of a strategy emerges. Large trials are a partial solution to this problem. The more participants there are, the more likely it is that a significant number of events will take place during the study period.

NIAID's largest, most expensive study to date, the ESPRIT trial, is enrolling 4,000 people for five years to test the effects IL-2, an immune stimulator. That trial is

costing \$43 million, including the establishment of a new international network of sites that could be used for other long-term strategy trials, too. At the January meeting, statisticians estimated that a when-to-start trial could require as many as 15,000 people and last a decade. Such a trial could cost over a billion dollars, according to one projection from what large-scale cardiovascular trials cost. Not all trials will have to be so big or unwieldy. But even a 6,000 person trial – the target enrollment for a “when-to-change” trial proposed by the CPCRA (see below) – handily outstrips ESPRIT in size. The network estimates that this trial will cost roughly \$29 million.

Concerns about cost and feasibility have led some activists to question whether these trials should be conducted at all. They point out that big-budget “blockbuster” trials will siphon money, participants and investigators away from other research projects. Any one of the trials will also bring the networks into uncharted waters in terms of enrollment targets, accrual rates, length and, potentially, large-scale international collaborations.

Can't Get Started?

Much of the controversy concerns when-to-start trials (WTSTs). A WTST would determine whether immediate treatment, regardless of CD4 count, improves the odds of disease-free survival over waiting to start therapy until CD4 counts dip below a certain threshold. A CD4 count of 250 cells/mm³ is one widely accepted cutoff point. WTST advocates say that a large-scale, randomized controlled trial is the only way to gather data that could reduce prescription costs and boost quality of life for countless HIV-infected individuals. But even the fiercest proponents of WTSTs admit that there are significant hurdles to designing and enrolling such trials. “Everyone agrees in principle on what the need is,” said Killen. “But there is a huge amount of disagreement about whether studies can be done.”

One of the chief obstacles for WTSTs is persuading patients and physicians to cede highly personal choices about medication to random assignment in a trial. Current research suggests that there may be real benefit to beginning treatment during acute infection, but it is not clear whether there is any additional benefit to starting drugs at CD4 counts above 250 during established infection. Short-term side effects and long-term toxicities of the drugs may prove detrimental to quality of life and survival time. As with cancer therapy, each doctor-

patient pair must consider medical facts, open research questions, untested treatments, and personal factors like age, income, children and likelihood of successful adherence.

For this reason, a WTST could be difficult to enroll. Many physicians and patients think that when to start is an important question to answer – many fewer are willing to put it to the test themselves. In 1992, San Francisco researcher Don Abrams initiated COMPACT, an early WTST, and is skeptical about the prospects for enrolling such a trial today. “The problem is there isn’t a huge amount of uncertainty in the patients and providers,” says Abrams. “They are not willing to leave it to the flip of a coin.” The Forum for Collaborative HIV Research is currently conducting feasibility studies. The Treatment Action Group (TAG) has also begun its own survey. Bill Duncan, Associate Director of Therapeutics Research at DAIDS, says that these studies will provide key guidance about how to proceed.

There are other issues, too. In order for a trial to take place, there has to be a clear, unanswered question. This elusive state of having no *a priori* opinion, or equipoise, is the foundation of clinical trial design. When it comes to WTSTs and equipoise, critics say it’s there – to a point. Cumulative data from observational cohort studies and other trials strongly suggest that it is safe to wait until falling below a CD4 count of 350 to begin treatment. British treatment guidelines use this level as the threshold for starting therapy; whereas United States guidelines set the bar at 500 CD4 cells/mm³.

Andrew Phillips, a British investigator, has presented retrospective analysis of data from the large EUROSIDA observational cohort. Phillips found that all treatment-naïve patients in the cohort had an equal likelihood of achieving maximal viral suppression as long as their pretreatment CD4 cell counts are above 200 and their viral loads below 100,000 copies/mL. Since a CD4 count of 200 may be the lowest acceptable limit for starting therapy, most WTSTs would likely set the threshold at 250. This raises the question of whether significant time, energy and money should be invested in paring down a zone of equipoise that, by some analyses, spans just 100 CD4 cells.

A CD4-cell count drop of 100 can take several years, and this is both a blessing and a curse. On the one hand, the wait boosts the relevance and importance of the WTST question. The interval lets people avoid the toxicities of HAART (highly active antiretroviral therapy) in the hope that less toxic drugs will be approved while

One of the chief obstacles for WTSTs is persuading patients and physicians to cede highly personal choices about medication to random assignment in a trial.

they remain off treatment. By the same token, the advent of new drugs could sway individuals in the deferred arm to leave the trial and start treatment. For those who wait until the predetermined time to start therapy, improvements in drug efficacy and tolerability could obscure the effects of waiting.

Trials and Test Cases

These issues and more came up in the debate over protocol PR306, an ACTG (NIAID's AIDS Clinical Trials Group) proposal that has been abandoned but is so far the only WTST to receive serious consideration. One version of the discussion draft of the protocol called for five-year follow-up of 2,400 individuals, who would be randomized into immediate and deferred treatment arms. Lower thresholds for initiating treatment were not finalized. A CD4 count of 300 CD4 was one proposed point for commencing treatment. Viral load over 100,000 copies was also considered as a signal to start. Death, AIDS-defining illness, CD4 count below 200 or Grade 4 drug toxicity were proposed primary endpoints. Possible secondary endpoints included undetectable viral load and complications of treatment.

In addition to the general criticisms of WTSTs, some viewed PR306 as not powerful enough statistically to answer its question. Spread out over five years, even a low rate of attrition could make it impossible to draw meaningful conclusions. Another concern was that the five years might not be long enough to measure a significant difference between the two arms. At a December, 2000 ACTG meeting, a clear majority of attendees voted against proceeding with the trial. Meeting attendees emphasized the importance of pursuing other options and approaches, including smaller, pilot studies or a trial that enrolls individuals with particularly confounding lab results, such as both high viral load and high CD4 cell count.

This no-confidence vote means that it may be some time before a U.S.-led WTST is launched. Reportedly, there have been no investigator-initiated grant proposals for WTSTs, and NIAID has not yet decided whether it will put out an RFA (request for applications). This step was supposedly part of NIAID's original plan for proceeding with long-term strategy trials.

In the meantime, other large-scale trial proposals are moving forward. NIAID is assembling review panels to consider two other large-scale trial proposals submitted by the CPCRA (NIAID's Community Program for Clinical Research on AIDS) and the VA (Veterans Affairs)

network. The CPCRA SMART trial will ask whether there is a benefit to being on treatment with CD4 cell counts above 250. SMART will enroll treatment-naive and treatment-experienced individuals. Those with over 250 CD4 T-cells will stop or defer treatment until their counts fall below this threshold. Individuals will stay on treatment until CD4 counts are above 350 on two consecutive visits and then will go off therapy again.

The VA proposal asks a management question about "loose versus tight" viral control. In one arm of the study, antiretroviral (ARV) therapeutic changes will be minimized unless viral load rises above a specific ceiling. The other arm will apply more stringent criteria, changing ARV in response to any evidence of viral replication above the lowest level of quantification. Target enrollment for this five-year study is 4,200 participants.

These proposed trials could provide guidance for long-term treatment management questions: How much viral control is needed to continue seeing the clinical benefits of a particular regimen? Must treatment be taken continuously to be effective, or can it be used as a time-limited, strategic intervention when CD4 cell counts begin to fall? What types of resistance will emerge and when? What strategies maximize the efficacy of a

given regimen? For the trials to enroll and retain target numbers of participants, these questions must remain relevant for the duration of the study. As much as possible, the study design must also be flexible enough to weather sea changes

in treatment choices. Limiting participants' drug options to those approved at the start date of the trial is unrealistic and could result in high dropout rates if participants are forced to leave the study in order to access a new, promising therapy.

Losing track of participants is one of the major hazards of long-term trials. For both WTSTs and strategy trials, planners must anticipate a situation in which new treatments and findings, or interim data from the study itself cause a large number of participants to leave the trial or deviate from protocol. It is impossible to anticipate all the shifts and developments in HIV research that could occur over a five or ten year period. Still, planners can make clear decisions from the outset about how interim data will be analyzed and presented to the public.

For long-term management trials to be feasible for and of use to doctors and patients, they must also reflect, as much as possible, the real world conditions of treatment use. Short-term data from clinical and observational trials of HAART show that adherence and success

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rates of regimens are higher in clinical trials. Those involved in the long-term efforts stress that the highly controlled model will not provide the desired answers. "We need to make trials less restrictive, more open to a broader range of people, and to do them under, as close as we can, real world conditions. It's moving away from drug development-type trials," said Jim Neaton, a CPCRA biostatistician and principal investigator of the ESPRIT IL-2 trial.

Growing Pains

Feasibility of long-term trials depends as much on network capacity as it does on the willingness of individual participants to enroll. Here too, there are open questions. The review panel assigned to SMART will have the additional task of evaluating the overall performance of the CPCRA network. The network, which has eliminated a number of low-performing trial sites in recent years, has yet to be re-funded by NIAID. It is currently receiving "bridge funding" for one year to cover its current efforts but will not be able to launch new studies until its network funding is renewed. Meanwhile, the VA's "captive" patient population should minimize loss to follow-up in long-term studies.

In addition to specific structural issues, both the ACTG and the CPCRA will have to deal with external factors, including managed care and financial incentives, which may lead investigators to choose for to participate in industry-sponsored trials. "As more and more patients go into HMOs, they may be less accessible to research," said Neaton. "In a way, health-care settings in Canada and Europe are more conducive to these trials."

For a WTST, U.S. networks will almost certainly have to team up with international partners to reach enrollment targets. Although the ACTG has partnered successfully with some overseas groups, treatment advocates point out that it does not have a strong background in this type of multisite, international effort. One possibility is partnering with developing countries such as South Africa, Brazil or

Thailand. A WTST would be much easier to do in these countries, which have both an adequate health-care infrastructure and large untreated populations with HIV. To do this, U.S. sponsors would have to navigate an ethical minefield, including issues of informed consent, relevance of the question to the study population, and availability of the drugs after completion of the trials.

Planners are also turning their attention to observational cohorts studies (OCS), which present far fewer obstacles to data collection. "We need to pursue randomized controlled trials," said Bill Duncan. "We also need to enhance existing cohorts. We need to pull them together and ensure that we are getting enough information, even with bias." OCS will be critical even after successful strategy trials are under way, said Alvaro Munoz, chief biostatistician for MACS (Multi-city AIDS Cohort Study). "Cohort studies are very well equipped to describe the treated history of individuals. They provide information on population effectiveness [of interventions] that these trials cannot provide."

As the debate continues, advocates and researchers agree that more education is needed to gain long-term commitment and public support for these trials. Particularly for a WTST, many U.S. communities will have to be swayed from the belief that it is unsafe to wait to treat, regardless of CD4 cell count. OCS data can help here, as can broader discussions about the lessons learned over the past four years of widespread use of HAART.

Four years of experience with HAART has proved insufficient to predict the long-term effects of these drugs on the heart, liver and kidney – or on HIV itself, which these regimens cannot completely suppress. As difficult as it is to conceive exactly how to make long-term trials work, it is even more difficult to imagine patients and physicians making a lifetime of treatment decisions based on educated guesses. "I'm hoping that what's done here is first in a generation of management trials that will incrementally improve how we take care of patients with HIV," said Jim Neaton.



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