Failure of Initial Antiretroviral Treatment Regimens

An update of Current Research

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The Forum for Collaborative HIV Research, (FCHR) situated within the Center for Health Policy Research (CHPR) at The George Washington University School of Public Health & Health Services, is an independent public-private partnership composed of representatives from multiple interests in the HIV clinical research arena. The FCHR primarily facilitates ongoing discussion and collaboration between appropriate stakeholders on the development and implementation of new clinical studies in HIV and on the transfer of the results of research into clinical practice. The main purpose of the FCHR is to enhance collaboration between interested groups in order to address the critical unanswered questions regarding the optimal medical management of HIV disease. By encouraging coordination among public and private HIV/AIDS clinical research efforts, the FCHR hopes to integrate these efforts into HIV/AIDS medical care settings. Therefore, studies performed by these various research entities, separately or in cooperation, can begin faster; duplication of efforts can be reduced; patient enrollment and retention can be further facilitated; and costs of getting answers to the critical questions can be shared. At present, the FCHR is staffed by three persons and consists of over one hundred members, representing all facets of the field. These include pharmaceutical companies; public and private third-party payors; health care delivery system groups; government agencies; clinical research centers; and patient advocacy groups. The Director of the FCHR is David Barr.

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Failure of Initial HIV Antiretroviral Treatment Regimens:

An Update of Current Research

A Monograph of the Forum for Collaborative HIV Research prepared by David Gilden

Many experts expect that HIV anti-retroviral treatment failure will be a growing problem since current antiviral regimens can control HIV replication without completely eliminating it. The implications of such “residual” replication for the evolution of drug resistance were a major point of discussion at the 12th World AIDS conference in Geneva. (‘Geneva’)

In June 1998, the Forum for Collaborative HIV Research (FCHR) issued a report on anti-retroviral treatment failure, providing an overview of research analyzing the following questions:
(1) how is treatment failure defined in current research? (2) How are estimates of treatment failure developed for studies? (3) What are the predictors of treatment failure? And (4) What are the results of studies of salvage regimens for patients who have failed therapy?

It might seem easy to define treatment failure and devise strategies to recover from it. Yet the causes of such failure remain murky and the consequent rescue or “salvage” strategies remain more the result of trial and error than any set guidelines. (Tentative salvage therapy guidelines are included in the HHS Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults, June 17 1998, table XIV.) A considerable amount of observation and practice is gradually accumulating, though, and a growing number of small trials have also explored the field. These new developments were outlined in the last four major biomedical conferences to focus on HIV: the 2nd International Workshop on HIV Drug Resistance and Treatment Strategies (‘Lake
Maggiore”), the 12th World AIDS Conference, the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the 4th International Congress on Drug Therapy in HIV Infection (“Glasgow”). This monograph will summarize the information from these meetings and serves to update the FCHR report of June 1998.

Types of Failure

There are three types of treatment failure. The first is virologic failure, which may be defined as either as lack of initial response to therapy, an incomplete response such that plasma viral load is reduced but remains above 400 or 50 RNA copies/ml, or later HIV rebound above 50 or 400 copies/ml. The obvious cause of virologic failure is viral drug resistance, whether existing prior to therapy or evolving in response to drug exposure. The role of drug resistance is not so straightforward, though. Notably, ACTG 343 - a study of maintenance therapy in which AZT/3TC or indinavir monotherapy replaced combination containing all three drugs after 24 weeks - observed an increased rate of HIV breakthrough in those switched to maintenance. But resistance to indinavir was never detected in the indinavir maintenance group. In the ACTG 343 participants with viral rebound while on triple therapy, only resistance to 3TC was observed. Other factors that may contribute to virologic failure include poor patient adherence to dosing schedules and poor drug absorption or pharmacokinetics that keep drug concentrations in the body from ever or only intermittently reaching suppressive levels. If the drug does not reach the virus, then inhibition fails even without the evolution of resistance-conferring mutations. More often, the HIV is exposed to suboptimal amounts of drug. This leads to viral replication at reduced levels with high risk of the eventual evolution of full-fledged, gene-based resistance.

One Dutch report indicated the critical role poor adherence plays in setting the stage for virologic failure by preventing drug from reaching the blood. Of 147 clinic patients supposedly
taking indinavir, 8.8% had no detectable indinavir in their blood and another 8.2% admitted to having taken their last dose longer than eight hours before their blood sample was drawn for drug level monitoring. (Indinavir should be taken every eight hours to ensure proper blood levels.) The investigators also examined 163 enrollees in a phase III indinavir clinical trial. Here, compliance was higher: only 1.8% had no detectable indinavir blood levels and 3.1% admitted to not having taken indinavir within the past eight hours. Finally, 25 patients specifically suspected of non-adherence were tested. Forty-four percent had no detectable indinavir. (There was no way to evaluate what percentage had taken their last indinavir dose more than eight hours before the clinic visit since these patients’ testimony was considered unreliable.)

The two other types of failure, immunologic (CD4 count decreases) and clinical (occurrence of new opportunistic conditions or death), appear to occur long after virologic failure has occurred. Studies in San Francisco and Switzerland have found increased CD4 counts up to a year after HIV either rebounded from unquantifiable levels or remained detectable in the presence of treatment.⁵,⁶ A German study also has looked at the predictive value of viral load and CD4 count in patients receiving protease inhibitor therapy.⁷ Treatment with protease inhibitors and higher CD4 count, but not lower viral load, independently correlated with reduced risk for disease progression. This suggests that either that profound but temporary viral load decreases protect against immune decline for a long period, or that the mutations that confer resistance to protease inhibitors somehow make for a less pathogenic virus. Viral load was a significant prognostic factor only for those not receiving protease inhibitors.

Other clinical observations illustrate how hard it will be to find salvage therapies that are effective in real world conditions. An analysis at the British Colombia Center for Excellence in HIV/AIDS⁸ looked at 50 people with advanced disease (mean CD4 count of 65 cells/mm³ and
mean viral load of 160,000 copies/ml) who were deemed “clinical” failures after long and complicated treatment histories. These individuals had HIV containing an average of four protease mutations and five reverse transcriptase mutations that conferred broad cross-resistance, making the success of any salvage therapy unlikely. The three that had “wild type” HIV had gone off therapy and probably harbored highly mutated subpopulations ready to rebound when therapy was restarted.

**When to Switch: Two Different Strategies**

Because of the temporal divergence between virologic and immunologic and clinical failure, researchers disagree over the proper time for giving up on current therapy and switching to a second line or salvage regimen. Also, the nature and goals of that regimen is a subject of debate. At ICAAC, John Mellors, MD, of the University of Pittsburgh gave an overview lecture that advocated early switching to a second line therapy as soon as possible after virologic failure was confirmed. Changing drugs soon would curtail the accretion of resistance mutations in HIV as it replicated more and more under the old regimen. Minimizing resistance mutations in turn would preserve many treatment options from the hobbling effects of cross-resistance and thus help ensure a good response to the rescue therapy. Generally speaking, the goal of salvage therapy would be the same as for first-line therapy: maximal suppression of viral load, as there is a strong correlation between viral load nadir and time to virologic failure. This last point was most recently repeated at the 4th International Congress on HIV Drug Therapy, by Julio Montaner, MD, of the BC Center for Excellence in HIV/AIDS, who grouped the results of three large studies testing nevirapine, indinavir or nelfinavir in treatment-naïve volunteers.

Jonathan Schapiro, MD, of Tel-Hashomer Hospital in Tel Aviv presented a dissenting view at ICAAC. While admitting the point that switching early would impede the evolution of
resistance and cross-resistance, Dr. Schapiro noted that in practice it is difficult to catch patients at just the right moment. In any case, treatment options are limited both by cross-resistance between drugs and the drugs’ individual toxic effects on individual patients. It might be better not to rush through all available drugs, exposing HIV to a series of not quite suppressive therapies in rapid order, but to maintain patients on a given regimen as long as they are immunologically or clinically stable even if viral loads are significant.

**Resistance Assays**

Resistance assays potentially can help doctors determine which drugs may still be active in a particular patient. A salvage therapy presentation at the 2nd Resistance Workshop\(^1\) illustrated the insights that may be gleaned by utilizing these assays. Phenotypic resistance testing helped explain the response of 18 persons to a four-drug combination during a salvage therapy study at San Francisco General Hospital. Eight volunteers who had failed to respond to an indinavir-containing combination were treated with abacavir/nevirapine/nelfinavir/Fortovase while another 10 received abacavir plus a second nucleoside analog and nelfinavir/Fortovase. (The volunteers had never received nevirapine or any other NNRTI.)

Notably, four of the volunteers turned out to have indinavir-sensitive HIV. No one had HIV sensitive to all four drugs in their regimen, but those with HIV still sensitive to two or three of the drugs in the combination experienced a profound reduction in viral load that reached a median of 2.5 logs (99.7%). The volunteers with HIV sensitive to zero or one drug had an immediate viral load drop that reached a median of 1.3 logs (95%) by the second week. This was as good as the first group had achieved at that point, but the second group’s viral load then rapidly returned to the baseline value.

A study from the British Columbia Centre for Excellence in HIV/AIDS\(^1\) checked the
predictive power of phenotypic resistance assays in 84 patients receiving ritonavir/saquinavir. Inability to respond to combination regimens containing these two protease inhibitors was highly correlated with phenotypic resistance to saquinavir, especially, but also to ritonavir to some extent. No person with HIV resistant to both attained viral loads below 500 copies/ml, the limit of detection with the viral load assay in use. But the patients whose tests showed sensitivity to both drugs did not always respond completely. Only about half the patients with prior protease inhibitors and test results indicating sensitivity to both protease inhibitors achieved viral loads below 500.

A study of the relation between genotype and response to salvage therapy (also a ritonavir/saquinavir combination) was conducted by Stanford University in 51 persons who had virologically failed a series of regimens that included multiple reverse transcriptase inhibitors and at least one protease inhibitor. Nineteen (37%) of the study participants attained plasma viral loads below 500 copies/ml while 18 (35%) had no virologic response at all. Failure was predicted by any combination of three protease mutations at codons 30, 46, 54, 82, 84, and 90.

French researchers recently presented very early results from the “VIRADAPT” trial, the first prospective data on the value of genotyping in selecting salvage regimens. The 108 participants were divided into two groups before their new therapy was selected. In the first group, doctors altered their patients’ regimen on the basis of personal experience and accepted standards of care. In the second, they received the results of the genotypic resistance assays. Of the 47 already followed for six months, 39% on the genotyping arm had viral loads below 400 copies/ml whereas only 9.5% in the standard-of-care arm had achieved this level. It should be pointed out, though, that the participants randomized to the standard-of-care arm turned out to have longer, more complicated treatment histories and more resistance-related mutations in their
HIV than the genotyped group.

Regardless of the eventual results of trials like VIRADAPT, resistance assays have yet to prove their worth under real world conditions, in which lab quality varies considerably. The ability of commercial medical laboratories to detect mutated HIV subpopulations will be crucial. Subpopulations making up as much as 25% of a person’s entire HIV can be easily missed. The majority of HIV in a patient may be deemed susceptible to a given drug, but if resistance exists in a minority of the HIV present, that minority will rapidly become the majority upon exposure to the drug and render it useless.

**Efficacy of Salvage Therapy**

The most ambitious salvage therapy trial to date is CNA2007, which enrolled 101 persons failing on their current regimens and gave them a triple combination that included the new drugs efavirenz (a nonnucleoside reverse transcriptase inhibitor or NNRTI), abacavir (a nucleoside analog) and amprenavir (a protease inhibitor). Of the 101 participants, 44% had never before received an NNRTI while 60% had received two or more protease inhibitors in the past. The median initial viral load was 123,000, and the median initial CD4 count was 160.

The overall response was not very good. At week 16, only about one-third of the participants had viral loads below 400 copies/ml. Response depended on the initial viral load and previous exposure to NNRTIs. 53% of those with an initial viral load below 40,000 and no prior NNRTIs had week 16 viral loads below 400 copies/ml. Three problems with this trial immediately arise: The first is the potential difficulty of adherence with amprenavir, which requires consumption of eight large capsules twice a day. The second is the interaction between amprenavir and efavirenz, which reduces amprenavir levels about 40% by inducing that drug’s metabolism in the liver. Toxicity fears also affected the results. Justifiably or not, many trial participants were taken off
abacavir because they experienced flu-like symptoms or skin rashes suggesting that they might be developing hypersensitivity reactions to the drug.

These same issues loom even larger in “mega-HAART” regimens, in which a maximum number of antiviral agents are administered concurrently. The hope is that enough of these compounds are at least partially effective and that in total, they will yield a significant suppression of viral load. A group of Frankfurt physicians have been administering six to eight drugs, including at least three nucleoside analogs, one or two NNRTIs and two to three protease inhibitors, to patients with a history of multiple viral breakthroughs on various regimens. The initial response in 37 patients has been promising, with 70% testing below 400 copies/ml on at least one viral load test. But it was difficult for most patients to continue on such a complicated regimen. Many had to switch to a simpler maintenance therapy, in which case their viral loads generally increased.

The British Columbia Centre for Excellence in HIV/AIDS reported on a similar mega-HAART study. Patients were treated with an individualized regimen containing five, six or more drugs (termed “Multi-Drug Rescue Therapy” or MDRT). 34% of the 55 patients achieved a viral load below 500 copies/ml at some point. In the two studies, viral load decreases correlated inversely with the extent of phenotypic or genotypic resistance. Still, there were responders in both Vancouver and Frankfurt who had multi-drug resistance.

Last winter, a group of doctors in St. Louis and St. Paul reported on using d4T/3TC/ritonavir/saquinavir to rescue persons with viral loads over 5,000 in three nelfinavir trials. The combination was very successful for the people who had been treatment-naïve before entering the nelfinavir trials (71% had viral loads below 400 copies/ml 24 weeks after switching), but much less so in those with greater treatment history and more advanced disease.
Since this report, a number of other small studies have looked at the role of double protease inhibitor combinations to rescue treatment failure. Double protease inhibitors often require more mutations in HIV before the virus can escape. If there is no HIV population in a patient containing all these mutations together, one PI covers the virus that is resistant to the other. Metabolic interactions between the two frequently raise their blood concentrations, too, making for a more potent attack.

Ritonavir/saquinavir was not that successful in either this study or in the San Francisco General Hospital one mentioned above, in the section on resistance assays. More recent reports give mixed results for the ritonavir/saquinavir combination when used in therapies following other protease inhibitors, particularly indinavir. In one French study of 67 persons previously on indinavir-containing combinations, only 7% had viral loads below 500 copies/ml at month 6, and this result was obtained using the bDNA assay. (bDNA gives viral load readings two to three times less than what the more popular Roche Amplicor assay would yield on the same sample, so the 7% figure is really for those going below about 1400 copies/ml.) Participants in this study were the hardest case imaginable. They had had either little initial response to the indinavir combination or had viral loads that returned to baseline after the initial response, plus they had previously received every available nucleoside analog. Some have suggested that doubling the saquinavir dose in this combination to 800 mg twice a day would have been more effective in such an extreme group.

In contrast, a retrospective chart review of 17 patients at Johns Hopkins who had failed regimens containing indinavir (13 persons) or nelfinavir (4 persons) found that 71% (12) achieved viral loads persistently below 400 copies/ml on ritonavir/saquinavir. This enhanced performance is probably due to the fact that the study participants had a relatively low viral load.
at the time of switching therapy (and, one may infer, fewer resistance mutations). The median viral load when going on ritonavir/saquinavir was only 13,500 copies/ml.

The use of nelfinavir as the single protease inhibitor in salvage combinations for people failing other protease inhibitors was not very successful in three observational studies probably due to the presence of prior protease mutations conferring cross-resistance to nelfinavir. In the best and largest (56 participants) of these uncontrolled, open-label studies, 36% achieved viral loads under 500 copies/ml, but this trial used the less sensitive bDNA assay.

On the other hand, the nelfinavir/saquinavir combination may be useful, at least temporarily. One representative study from Germany used a four-drug, twice-a-day regimen consisting of two nucleoside analogs plus nelfinavir (1250 mg bid) and saquinavir (1000 mg bid) in 25 patients who had failed at least one protease inhibitor-containing triple combination. The median baseline viral load was a relatively low 20,000. The proportion of patients with plasma RNA levels below 500 was 60% at week 8 but only 45% at week 24. Likewise, another small German study of nelfinavir/saquinavir (plus d4T) rescue observed its cohort’s viral loads drop over the first four weeks from a median of 149,000 to 45,000 copies/ml, but then the median viral load returned almost to baseline by week 12.

Double protease inhibitor combinations involve taking at least four, usually more, different drugs (including two complementary nucleoside analogs), which makes for an onerous dosing schedule and risks introducing multiple drug-related toxicities. One of the original salvage therapy studies used only the nonnucleoside reverse transcriptase inhibitor nevirapine in combination with 3TC and indinavir to create a relatively successful and nontoxic combination for rescuing failed nucleoside analog regimens (one person of the 22 study participants had received ritonavir and two had prior loviride). A number of other studies have
tried using efavirenz or nevirapine plus a protease inhibitor in persons with long histories on nucleoside analogs but no experience with NNRTIs or protease inhibitors. Among the first was a study by Gail Skowron of Brown University using d4T/nevirapine/nelfinavir in which 16 of 19 (84%) volunteers had a viral load below 400 by week 9.\textsuperscript{32}

Two DuPont studies treated the same population with efavirenz and two nucleoside analogs plus either indinavir (DuPont protocol 020)\textsuperscript{33} or nelfinavir (DuPont protocol 024).\textsuperscript{34} At week 16, the percent of the cohort remaining on treatment who had viral loads less than 400 was 85% and 63%, for the indinavir/efavirenz and nelfinavir/efavirenz combinations, respectively. The two protocols at 16 weeks were still following 71 and 26 volunteers, again respectively.

A larger study, ACTG 364, also was presented at Geneva.\textsuperscript{35} It followed 196 individuals with viral loads over 500 despite long treatment histories on various nucleoside analog regimens in two other ACTG trials (no protease inhibitors or NNRTIs). The median viral load at the start of the study was very low, 7626 copies/ml. Study participants were randomized in blinded fashion to receive two, preferably new, nucleoside analogs plus either nelfinavir, efavirenz or both. At 16 weeks, the percent with viral loads below 500 was 64% for the nelfinavir arm, 69% for the efavirenz arm (a non-significant difference) and 81% for the arm with both agents (a significant difference with the nelfinavir arm).

Then there was the comparatively major CNA2007 protocol using the efavirenz/abacavir/amprenavir combination described above. It was conducted in a cohort that was heavily experienced in both nucleoside analogs and protease inhibitors. The triple regimen of experimental drugs only performed respectably in the volunteers without prior NNRTIs.

A number of preliminary studies, some no more than chart reviews, have tried using nevirapine plus a protease inhibitor and one or two nucleoside analogs in similar populations.
Typical is one London hospital study\textsuperscript{36} in which doctors prescribed nelfinavir plus nevirapine and nucleoside analogs to 19 patients who had previous protease inhibitors but no NNRTIs and viral loads greater than 10,000 copies/ml. In 17 of the 19, the nucleoside analogs were merely continued or recycled from past therapies, and the response was not great. Only five of the 19 (26\%) had viral loads below 400 copies/ml at 24 weeks.

Another newcomer that has been tried in salvage therapy is the nucleotide analog adefovir from Gilead Sciences. The company’s protocol 408\textsuperscript{37,38,39} added adefovir onto current therapy in 429 volunteers with a mean baseline viral load of 72,000 copies/ml and a mean baseline CD4 count of 352 cells/mm\textsuperscript{3}. The volunteers were allowed to switch background therapy at will. About 17\% of the 182 persons receiving adefovir for 24 weeks had viral loads below 500 copies/ml, compared to 5\% in the placebo arm.

According to a Gilead genotypic substudy, the reverse transcriptase codon 184 mutation that makes HIV resistant to 3TC paradoxically increases the virus’s sensitivity to adefovir. Conversely, adefovir has no effect on HIV with the mutations that confer high-level AZT resistance. But how many people have HIV that has been exposed to 3TC and not AZT? About 15\% of the 142 persons in the protocol 408 substudy had HIV resistant to 3TC but not AZT. These people’s viral loads declined by an average of .94 logs (89\%) at 24 weeks. 53\% had high-level resistance to both AZT and 3TC, and they exhibited a modest viral load drop of .5 logs (70\%) at 24 weeks. (Worse yet for adefovir, 32\% of protocol 408’s participants who had been on adefovir for 48 or more weeks developed signs of serious renal dysfunction and had to stop the drug.)

Another possible innovative salvage strategy involves hydroxyurea, which purportedly circumvents the drug-resistant HIV issue by constricting the production of natural nucleosides...
for assembly into DNA and thus makes the nucleoside analogs much more potent. The British Colombia center included hydroxyurea in its MDRT combination mentioned above. A UCLA chart review described how 18 heavily pretreated patients fared on a d4T/3TC/hydroxyurea combination. Despite having HIV with d4T and 3TC resistance mutations, the 18 patients had a median peak viral load reduction 1.7 log (98%) by week 8. The average length of time with at least a .7 log (80%) viral load reduction was 17 weeks. This regimen seemed to elicit a strong but temporary response and, besides, frequently caused severe bone marrow suppression.

Conclusion

Given the availability of NNRTIs and protease inhibitors, it is not too difficult to rescue people whose treatment history includes only nucleoside analogs. Recent reports make clear, however, that persons with more complex treatment histories develop HIV with extensive cross-resistance to drugs in all classes and are much more difficult to rescue. As the years of managing HIV infection without achieving eradication accumulate, the need for such rescues will increase. The capacity to resort to second- and third-line combinations should be part of the treatment plan elaborated when a patient first starts therapy. A number of ACTG trials are investigating the most effective salvage regimen sequencing under specific conditions, but long-term management trials may be the only way to have any assurance about the validity of sequential treatment plans for individual patients in the clinic.

22 Clotet B. 4th International Conference on Drug Therapy in HIV Infection, Glasgow; Nov. 8-12 1998. Satellite Symposium 3 (sponsored by Hoffmann-La Roche).