DEAR READER

Salvage is an ugly word. Saying it by itself, one thinks of a large yard with rusting heaps of old appliances or dismantled cars that once had use and purpose in our modern world. Salvage can also refer to the rescue of a ship from a shipwreck, fire, or other destruction. So, how in the world could we have ever applied such a word to people living with HIV/AIDS? Perhaps it's the meaning of salvage as a verb—to save from loss or destruction. But is that any more appropriate?

Medical jargon is filled with examples of dehumanizing and insensitive terminology, created largely for purposes of convenience and, less convincingly, practicality. How many of us cringe when we hear about "cancer patients" or "AIDS patients" instead of "patients with cancer" or "people living with AIDS," as if one's disease defined a human being? Those are by far among some of the least offensive examples. Therefore, considerable burden or even stigma might be attached to the use of phrases like "salvage patients" or even "salvage therapy" to refer to the situation where cross-class viral drug resistance abounds and treatment options to suppress virus and restore immune function are in desperate need.

But given one of its meanings is synonymous with "rescue," the use of "salvage" might be justifiable. What are the alternatives? Highly antiretroviral treatment-experienced? Multi-drug resistant? Such lengthy or technical phrases do not impart the urgency associated with this condition. Language is a powerful tool, and the ability to express such a profound concept in just one word can be very effective.

The reality of patients who need salvage or rescue therapy has been apparent from the very early days of HIV therapy. These are patients who will experience disease progression and die unless something is done. With each enhancement in antiretroviral therapy over the past 15 years or so has come the acute reminder that this virus presents a formidable challenge and will not easily be subdued or eradicated. Salvage therapy represents our failures in HIV therapy thus far. Salvage patients remind us that we must not settle for anything short of a cure.

I write this letter in the midst of hearing about the loss of Charles Clifton, a colleague, a friend, and an inspiration. Charles was the Executive Director of Test Positive Aware Network (TPAN) in Chicago and Editor of its publications (***www.tpan.com***). He also served with me on the Steering Committee of the AIDS Treatment Activists Coalition (***www.atac-usa.org***). His presence in AIDS advocacy will be sorely missed; his humanity and service will not be forgotten. This issue is dedicated in Charles Clifton's memory. Farewell, Charles.

Very truly yours,
The Center for AIDS:
Hope & Remembrance Project

Thomas Gegeny, MS, ELS
Senior Editor

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OVERVIEW

Salvage Therapy II Think Tank

April 16–17, 2004

Houston, Texas

Sponsored by

The Center for AIDS: Hope & Remembrance Project (Houston)

and

Forum for Collaborative HIV Research (Washington, DC)

with local planning partner

The Center for AIDS Research (CFAR) at
Baylor College of Medicine and The University of Texas Health Science Center

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Additional thanks to Betty Slagle and Dede Fox of Baylor College of Medicine.

This meeting was dedicated in memory of L. Joel Martinez, 1953–2003.

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Mike Youle, MD
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HIV Medicine

Program in brief

Friday, April 16, 2004

12:00 pm Registration/sign-in; Lunch

1:15 pm Welcome and introductions
Thomas Gegeny

1:30 pm Session 1: Recap of '99 meeting
Presentation by Trip Gulick

2:30 pm Session 2: Clinical research in the salvage setting (I)
Presentation by Miklos Salgo

3:15 pm Break

3:30 pm Session 2: Clinical research in the salvage setting (II)
Panel discussion moderated by Trip Gulick

5:30 pm Close of Day 1

6:45 pm Dinner

Saturday, April 17, 2004

8:00 am Breakfast

8:30 am Session 3: Clinical management issues in the salvage setting
Presentation by Joel Gallant
Panel discussion moderated by Thomas Campbell

10:00 am Break

10:15 am Session 4: Do we have new tools?
Presentation by Richard Ogden
Panel discussion moderated by Richard Haubrich

12:15 pm Lunch

1:00 pm Session 5: Novel strategies
Presentation by Steven Deeks
Panel discussion moderated by Ben Cheng

2:30 pm Session 6: Adjourn to break-out panels

Panel 1: Integrating salvage research into existing networks/structures (clinical trial networks, observational cohorts, industry-sponsored programs).
Moderated by Daniel Kuritzkes

Panel 2: Proof of concept studies/ translational research; new hypotheses.
Moderated by Kimberly Struble

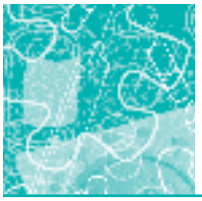
Panel 3: Future of Salvage Therapy: Monitoring systems for patient outcomes. Will the needs change in the next decade?
Moderated by Doug Ward

Panel 4: Regulatory Issues and challenges in salvage therapy
Moderated by Trip Gulick

4:00 pm Final discussion
Moderated by Veronica Miller

5:30 pm Close of Day 2

7:00 pm Dinner; Departures



The Salvage Therapy II Think Tank

By Jennifer Newcomb-Fernandez, PhD

On April 16 and 17 of 2004, the "Salvage Therapy II Think Tank" was held at the Baylor College of Medicine in Houston at the Texas Medical Center. This meeting was co-sponsored by The Center for AIDS (CFA) and the Forum for Collaborative HIV Research. The Center for AIDS Research (CFAR) at Baylor College of Medicine and at The University of Texas Health Science Center at Houston was a local planning partner. This meeting was dedicated to the memory of L. Joel Martinez, the founder of The CFA, who passed away in November 2003. The goals of "Salvage Therapy II" were as follows:

- To bring together relevant groups with the goal of establishing priorities and objectives for increasing the effectiveness of medical care, the quality of life, and the survival of highly treat ment-experienced ("salvage") patients with HIV/AIDS.
- To identify areas of basic science and clinical research that might translate into the development of treatments or the establishment of useful clinical care guidelines for the medical management of salvage patients.
- To facilitate initiation of research collaborations among the various participants and to explore ways to build a national network of research collaborators for implementing these research priorities and objectives.

Participants at the meeting were from a variety of backgrounds and organizations, including HIV/AIDS community advocates; HIV-treating physicians; scientists working in the fields of HIV and immunology; and representatives from pharmaceutical companies, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the European Medicines Agency (EMEA). This gathering allowed an interdisciplinary dialogue offering several different perspectives on the state of salvage therapy. The meeting's format comprised plenary presentations and panel discussions, and participation from all attendees was encouraged.

1999: SALVAGE THERAPY MEETING

The Salvage Therapy II Think Tank was a follow-up to "The Challenges of Clinical Trial Design in Assessing the Effects of Anti-HIV Therapy in Heavily Pre-treated Patients," a meeting held in May 1999. A report from the 1999 meeting is available at the website of The Forum for Collaborative HIV Research (***hivforum.org/publications/clinicaltrial_design.pdf***). Roy (Trip) Gulick, MD, MPH, from Cornell University, chaired this first meeting and provided a recapitulation at the 2004 meeting. At the time of the first meeting, patients had access to 14 approved antiretroviral drugs. As use of protease inhibitors (PIs) increased, the number of deaths attributable to HIV infection was decreasing dramatically.[1] Consequently, more people were living with HIV infection and taking combination antiretroviral therapy. Dr. Gulick emphasized how "the reality of these therapies began to sink in" as large cohort studies across the US and Western Europe began to report that, in contrast to data collected in clinical trials, about half of the patients seen at these clinics were failing therapy despite taking state-of-the-art combination therapy.[2-6] Clear and effective strategies were necessary to deal with this chal-

lenge. The Department of Health and Human Services (DHHS) released guidelines in 1999 recommending that a patient's regimen "be changed entirely to drugs that have not been taken previously. . . . at least two and preferably three new drugs should be selected that are not subject to anticipated cross-resistance." This was obviously a challenge with only 3 classes of drugs available. These guidelines also failed to adequately account for variable cross-resistance such that *new* drugs did not necessarily mean *effective* drugs.

Several studies began investigating possible salvage regimens with very disappointing results, with only about 26% to 37% of patients able to suppress viral loads.[7-10] This environment was the backdrop of the first meeting in 1999, the goals of which were as follows:

- To discuss the design and implementation of studies of salvage therapy regimens in heavily pre-treated patients.
- To present needs, priorities, and challenges faced by industry, researchers, regulators, and patients.
- To define treatment failure and success.
- To understand and agree on what is necessary and feasible when designing studies of new drugs for salvage therapy.

Meeting participants discussed the numerous obstacles to developing successful salvage options. These barriers included a heterogeneous patient population and a lack of 1) clinical studies addressing salvage therapy, 2) standard of care guidelines (ie, when to change therapy) and definitions (eg, virologic failure), and 3) pharmacokinetic (PK) and drug interaction data. Existing clinical trials had a small likelihood of success and a potential for causing increased drug resistance among participating patients. Several challenges were identified concerning the complicated logistics of conducting multi-agent studies. Much discussion centered on the distinction between assessing individual agents versus a combination regimen. Industry representatives believed there was little incentive to participate in multi-drug studies. Specifically, they were concerned about the effect of negative data on the approval process and the maintenance of confidentiality between companies. Regardless of these obstacles, Dr. Gulick noted, "the salvage setting is the greatest challenge and the greatest need in our clinics," words he spoke at the first meeting in 1999 and repeated again in 2004.

Participants agreed the best way to find effective therapies for this population was through more clinical trials and data collection. Specifically, the consensus was to utilize resistance testing and therapeutic drug monitoring (TDM), and to assess PK and drug interaction data early in the drug development process. Participants also discussed novel study designs that would allow examination of several new agents while patients still received the standard of care. Recommendations included short-term studies to evaluate virologic response, specifically designing multi-stage nested studies whereby patients would receive a single agent for 1 to 2 weeks and then a combination regimen for 24 to 48 weeks. In this type of design, virologic response to a particular agent could be assessed quickly over a matter of weeks while safety and efficacy of the combination regimen could be analyzed over several months or years. The idea of using structured treatment interruptions (STIs) in this patient population was also considered. Importantly, the FDA representatives encouraged industry representatives to evaluate their therapies in different patient populations, including heavily pretreated patients, and acknowledged that there was a different risk:benefit ratio in this type of patient compared with treatment-naïve patients.

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2004: SALVAGE THERAPY II THINK TANK

Fortunately, there have been some advances in the area of salvage therapy since the 1999 meeting. In January 2001, the FDA convened an Antiviral Drug Products Advisory Committee meeting to specifically address the challenges of designing salvage studies and developing investigational agents for salvage therapy. On March 23, 2004, updated DHHS Guidelines (available at ***aidsinfo.nih.gov***) were released supporting "the strategy of . . . designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral agents for the new treatment regimen." Joel Gallant, MD, from Johns Hopkins University School of Medicine, explained that today, resistance testing is wisely and commonly used in the setting of clinical failure. A benefit realized by all HIV-infected patients today is the increased number of approved antiretroviral agents and the number of drugs advancing through the drug development pipeline. (Though, if none of the drugs work in treatment-experienced patients, then such agents offer little advantage to these patients.) The use of other agents, primarily ritonavir (Norvir), as a PK boosting agent in antiretroviral regimens is common practice today. Clinical studies have been conducted in which short-term PK studies are nested in longer-term studies (eg, ACTG 5143). In addition, a few multi-agent studies have been conducted (eg, ACTG 398, ACTG 5118). The two-part hybrid study design is also used in salvage therapy studies where a new agent is tested for 1 to 2 weeks and then combined with an "optimized background" therapy (OBT).

Unfortunately, many of the challenges and obstacles facing the patient and physician in 1999 still exist. With the exception of the studies discussed below, there have been few clinical trials focused on regimens for highly treatment-experienced patients. Dr. Gulick summarized the situation by noting that in 1999, patients had 2 chances to achieve sustained viral suppression. Now they have 3. The lack of clearly defined study endpoints and standard guidelines for patient care slows progress in this area. Though many agents are in the drug development pipeline, it is not yet clear if they will benefit the highly treatment-experienced patient. Ensuring these patients have access to multiple effective agents is absolutely critical. For a variety of reasons, this access is frequently not available, forcing patients into an archaic cycle of sequential monotherapy.

The TORO studies

The TORO1 and TORO2 trials are examples of clinical trials specifically designed for salvage patients. These trials led to the FDA approval of enfuvirtide (Fuzeon or T-20), the first drug developed specifically for use in salvage. Miklos Salgo, MD, PhD, from Hoffmann-La Roche, Inc., explained that while designing these studies, he and his colleagues struggled with many of the issues raised at the first salvage therapy meeting. In addition, numerous consultations were made with HIV patient advocates and experts in the field of HIV medicine, as well as regulatory authorities. Dr. Salgo noted that to have clinical relevance, the study population had to reflect the patient population likely to use the drug in clinical practice. In this case, this was the treatment-experienced patient, a type of patient typically not included in clinical trials at that time.

Several challenges existed because of the complex needs of this patient population. Conventional efficacy endpoints (eg, the proportion of patients with virus below the level of detection) and common definitions of treatment failure were not appropriate for these advanced patients, forcing the researchers to construct novel criteria for this study. Moreover, patients received an individualized optimized background (OB) because a standard fixed-drug background might not be as effective. The use of geno-

typic and phenotypic viral resistance testing ensured that patients received the best possible background regimen. Patients were permitted to include 2 investigational antiretrovirals, lopinavir/ritonavir (Kaletra) and tenofovir, which were available in expanded access programs at the start of the trial, as part of their OB regimen. Study participants were randomly assigned to an OB arm (control group) or OB plus T-20 arm, but were permitted to switch to the T-20 arm if they experienced virologic failure on the control arm. This "switch design" created challenges in the safety assessment because the control arm dwindled as the study progressed. Regardless of these complications, Dr. Salgo believes these studies were patient friendly, medically and scientifically sound, and statistically robust. However, concerns were raised by others that studies of any new drug in patients with virus exhibiting multi-drug resistance (MDR)—a major characteristic of patients in salvage situations—might force patients into sequential monotherapy. Dr. Salgo reasoned that the provision of viral resistance testing at screening and allowing use of 2 other investigational agents as part of the OB regimen were practical steps incorporated into the TORO studies to minimize the risks to patients.

Lack of standard of care guidelines and definitions

A major hindrance to progress in salvage therapy is the lack of standardization in patient care guidelines and definitions of terminology. This patient population is extremely heterogeneous with different treatment histories, resistance profiles, and afflictions—features that complicate the task of designing clinical trials. As debated by several participants, the lack of universal definitions confuses the salvage therapy arena, making comparisons between trials difficult.

Indeed, Jeff Murray, MD, MPH, from the FDA commented that there is still no clear and universal definition of "salvage patient," a point also noted by Nathalie Morgensztejn from the EMEA. At the 2001 Antiviral Drug Products Advisory Committee meeting, participants agreed that patients who experienced a loss or lack of virologic response with at least 2 highly active antiretroviral treatment regimens (HAART) and 3 classes of drugs were considered to be in salvage. However, with the introduction of a fourth class of antiretrovirals (entry inhibitors), this definition is now outdated. In addition, there are still no clear definitions for treatment success or failure in the salvage population. For example, is complete virologic suppression a requirement for treatment success? Is study success synonymous with clinical response? Matt Sharp from Test Positive Aware Network in Chicago, a long-term HIV-positive survivor and TORO participant, pointed out that while he "failed" treatment according to study definitions, he experienced a clinical response on T-20 and is a "salvage therapy success story."

Further complicating this situation is that there are no standard guidelines on how to treat the salvage patient population. While we now know that patients must switch to at least 2 effective drugs once their previous regimen fails, physicians do not fully understand if and when to switch patients. Unfortunately, some physicians may not have the clinical experience or education to recognize the importance of cross-resistance. They fail to note that new drugs do not always equate with new options in treatment-experienced patients with MDR. In the absence of efficacious therapeutic options, some clinicians will keep patients with MDR on a failing regimen that may provide some virologic stability and decrease the loss of CD4 T cells. Dr. Gallant pointed out the pros and cons of this approach (see Figure 1).

A patient management issue that is still under debate is whether dual-boosted PI therapy is beneficial in the salvage population. This strategy could

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be used in situations where patients have no adequate nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) options. Disadvantages of this strategy include high pill burden and potential for increased drug toxicity. Though this approach is used in many patients, physicians have little guidance. Steven Deeks, MD, from the University of California at San Francisco, commented that his patients did not want to participate in this type of treatment regimen because of concerns over increased toxicity. It is still unclear whether a dual-boosted PI approach at standard doses is advantageous compared with higher-than-normal doses of one boosted PI. Calvin Cohen, MD, from Harvard Vanguard Medical Associates, commented that this issue is more complicated than comparing a single PI versus 2 PIs and requires an understanding of the specific viral patterns suppressed by a dual-boosted approach versus those that are suppressed by one boosted PI. Further exploration is required as these questions have not been answered adequately. Unfortunately, pharmaceutical companies have shown little interest in conducting the necessary clinical trials.

Another potential approach to treating salvage patients is intensification. The pivotal studies leading to initial approval of tenofovir (Viread) were intensification studies. In an intensification strategy, the addition of another active agent is used to bolster a patient's existing regimen (eg, adding a fourth drug to intensify a 3-drug regimen). For some patients, particularly those with modest viremia, this approach may lead to sustained viral suppression and prevent or delay the development of drug resistance. The downside of this strategy is that it only exposes patients to a single new agent. If the viral load is not completely suppressed, this may result in rapid loss of efficacy of the newer drug. The meeting consensus was that this is not an ideal design.

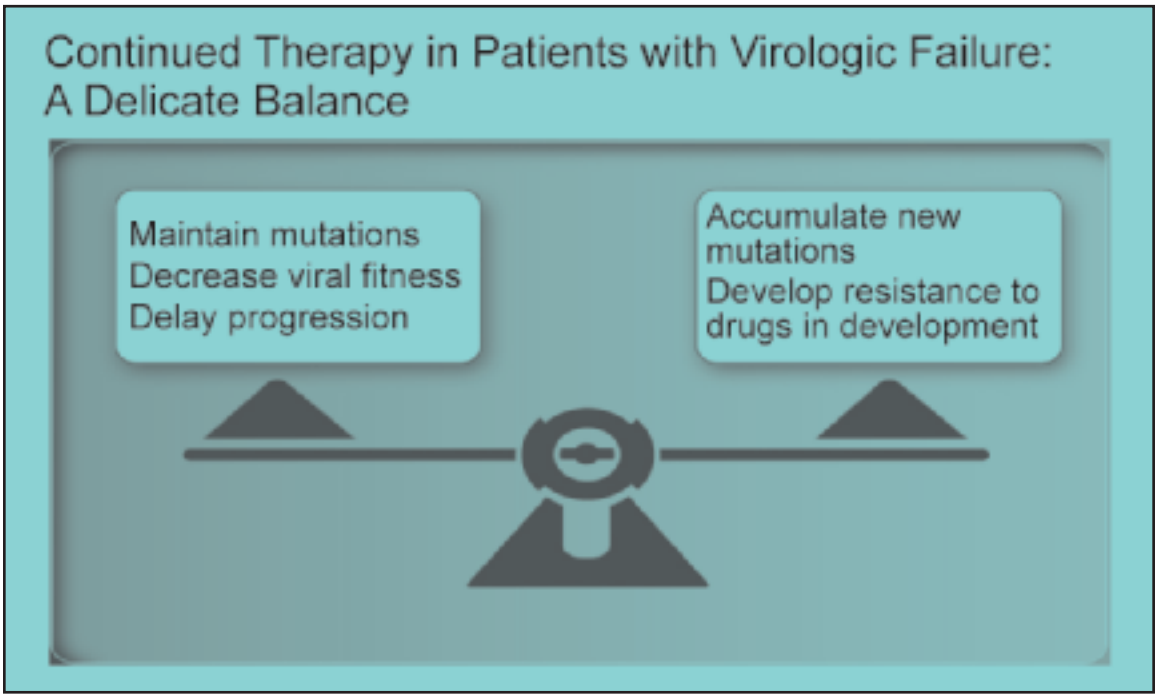

Figure 1. **The challenges of continued treatment in salvage patients as presented by Joel Gallant**

Whether or not treatment interruptions could be beneficial when switching salvage patients to a new regimen was also a point of discussion and was reviewed by Dr. Gallant during his presentation. The concept of STIs in this patient population stems from the hypothesis that interrupting treatment may allow a rebound of wild-type, drug-susceptible virus. Temporary re-emergence of drug-susceptible viral strains, while transient, may provide an opportunity for salvage therapy to work with some increased efficacy. As pointed out by Dr. Gallant, the results of clinical trials assessing this approach are conflicting (see the Fall 2003 issue of RI*TA!* for more discussion: ***centerforaids.org/rita***). Some smaller studies have reported positive effects of STIs prior to initiating salvage therapy,[11-13] while more recent data suggest that interrupting treatment is associated with no benefit and may in fact be harmful.[14,15] Factors responsible for the disparate results include duration of interruption, intensity of salvage regimen, shift to wild-type virus, and patient adherence. The OPTIMA trial (OPTions In Management with Antiretrovirals) is a large, randomized, multi-center, controlled trial investigating the effects of interrupting treatment in patients taking mega-HAART (comprised of 5 to 9 antiretroviral drugs) or standard HAART. This study is currently enrolling patients in the US, United Kingdom, and Canada.[16] By contrast, other investigators felt that prior large, randomized STI trials have disproven the concept of viral reversion improving the response to therapy. However, some improvement in adherence may result from allowing patients a break prior to initiating highly complex regimens (eg, GigaHAART).

Challenges to conducting clinical trials in the salvage population

The challenges of conducting studies in salvage populations were discussed at length throughout the conference. Few clinical trials are currently addressing salvage therapy. As discussed above, the extreme heterogeneity of the patient population introduces numerous complications that do not need to be addressed when studying treatment-naïve patients, most notably the need for individualized OBT. In addition, if a "switch" to the experimental arm is permitted (and researchers believe this option should be available to salvage patients), assessing safety is problematic because the control group is whittled away as the study progresses. Therefore, long-term safety comparisons with the control arm are virtually impossible. Whether clinical trials should focus on testing drugs in treatment-naïve or salvage patients before approval was also discussed. Because more salvage therapy options are desperately needed, should clinical trials initially focus on this patient population? There was obvious concern by the industry representatives that if testing is not successful in salvage patients, the approval process could be jeopardized.

Much discussion centered on the timing of these studies. While participants agreed that drug activity could be determined fairly quickly, with studies as short as 12 weeks or less, confirmation of safety requires more time because serious adverse events and drug interactions may not be evident as quickly. Initially establishing the safety profile for an individual drug is important before combining it with other effective agents to understand which drug is causing a particular side effect. But for how long should a drug be studied before it is considered safe, even in the salvage population? Recommendations from meeting participants ranged from 24 weeks to 1 year. Finally, in this scenario, when does a company perform the necessary PK studies? For patients to have access to new drugs and make informed decisions about combining antiretrovirals, PK data examining potential drug interactions with other antiretrovirals or common concomitant drugs is crucial. As more drugs are developed, there will be more potential combinations and thus the number of desirable interaction studies will grow exponentially. Understandably, pharmaceutical companies do not want to

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conduct these interaction studies until an experimental drug is shown to be effective and safe, which could take many months. From their perspective, until they know an agent has a good chance of obtaining approval, there is no reason to conduct such studies.

A recurring discussion was the lack of multi-agent investigational trials. Because salvage patients are best treated with at least 2 effective agents, studies with multiple experimental agents would seem ideal. However, as new agents are typically in different stages of development, it is a formidable challenge for a single pharmaceutical company to conduct a clinical trial with 2 new such agents. As a result, studies with multiple experimental agents most likely will require the cooperation of 2 (or more) pharmaceutical companies. For a variety of reasons, companies are wary about working together and sharing confidential information. A major concern is that the toxicity of one drug will be generalized to the entire regimen, deeming both investigational agents as dangerous. Even potential situations where one drug is shown to be "good" and the other as "great" can cause anxiety for these companies. The "good" drug may appear less than optimal, or even ineffective, but may provide the support to make the other drug "great." The logistics of designing and conducting clinical trials with 2 sponsors may seem daunting because of legal and proprietary concerns on the part of industry. However, conducting such trials through a third party (such as a research institution or clinical trials network) may be one potential solution.

The "modified" multi-factorial design (see Table 1) was discussed at length during the first salvage therapy meeting, but has since been deemed unrealistic by many researchers because of the challenges associated with including multiple new agents in one study. While the chances of having 3 investigational agents to include in one trial design are unlikely, the odds are better with 2 investigational drugs. As with concerns about sequential monotherapy in patients with MDR virus (such as with the TORO studies), most patients enrolled into a modified factorial study design with 2 new agents only receive one new drug in addition to OBT. However, the opportunity for subjects to receive 2 new agents may be possible if 3-class-experienced, T-20-naïve subjects are randomized to receive Drug X + OBT vs Drug Y + OBT vs Drug X + Drug Y + OBT when OBT includes T-20.

Expanded access and compassionate use

The HIV patient advocacy community is extremely discouraged with the complexities involved in providing experimental agents for compassionate

Table 1. Modified, multi-factorial clinical trials designs

For 2 investigational drugs (X and Y)	For 3 investigational drugs (X, Y, and Z)
Drug X + OBT	Drug X + Drug Y + Drug Z + OBT
Drug Y + OBT	Drug X + Drug Y + OBT
Drug X + Drug Y + OBT	Drug X + Drug Z + OBT
	Drug Y + Drug Z + OBT
	Drug X + Drug Y + Drug Z*

OBT = Optimized Background Therapy
Standard of care (SOC) assumed.

* May not be possible depending on drug classes, resistance, etc.

use and felt this issue was not adequately addressed at the meeting. Because of the lack of approved and effective agents for salvage therapy, patients with no other options (and who are excluded from most clinical trials of new agents) have no good means for accessing these drugs before FDA approval. Activists emphasized the different risk:benefit ratio for these types of patients and that the inability to obtain access to 2 new agents at the same time was perpetuating treatment failure (for instance, patients who are enrolled in a clinical trial of an experimental antiretroviral agent are often prohibited from also taking agents in expanded access, which are usually in late-phase clinical investigation).

Participants debated over which information was necessary before drugs could be released into expanded access or compassionate use programs. As discussed above, are extensive PK and interaction data required for these patients as they will be taking the new drug in combination with other antiretrovirals? Representatives from industry pointed out that access may necessarily be limited early in the drug development process, not only because efficacy and safety data are lacking, but because drug dose may not be determined yet and large-scale manufacturing may not be available. Nevertheless, is the lack of extensive safety data legitimate grounds for delaying access to patients with no other options? Participants also discussed the barriers that exist when trying to obtain expanded access and compassionate use for patients. HIV-treating physicians explained that the administration associated with expanded access programs is enormously time consuming and takes away from funded clinical research. The FDA has few requirements other than the reporting of serious adverse events. However, institutional review boards (IRBs) and pharmaceutical companies require extensive data collection for each patient, resulting in large amounts of paperwork.

While patient safety was one of the main reasons cited for delaying drug access, Daniel Kuritzkes, MD, from Brigham and Women's Hospital, described other risks and costs to research that can occur when access is provided too early in the drug development process. For example, preclinical data suggesting that a side effect *may* occur in a patient necessitates comprehensive evaluations that complicate the study design and data collection. Other disadvantages include harming the investigators' and university or hospital's reputations if a patient experiences significant or fatal side effects. These types of situations can slow down the approval process considerably. One industry representative pointed out that pre-approval access can interfere with the efficiency of enrolling patients in a Phase III program, as well as potentially delay the approval process, because studies will have difficulty enrolling patients.

DRUGS IN THE PIPELINE: SECOND-GENERATION HAART

NRTIs, NNRTIs, and PIs in the pipeline

As explained by Richard Ogden, PhD, from Agouron/Pfizer, the decision for companies to work in the salvage setting is not to be taken lightly because of the numerous challenges discussed above. However, he believes, as do other industry representatives, that there is a compelling need and responsibility to develop drugs for these patients. Several companies have compounds in development from existing drug classes (ie, NRTI, NNRTI, and PI), though the therapeutic advantage of these agents is only of value to salvage patients if they have unique resistance profiles. Unless the drug is active against common MDR strains, other benefits such as improved dosing or less serious side effects are of limited benefit to salvage patients. However, some drugs in development may provide additional treatment options for this patient population

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because they have shown activity against drug-resistant HIV. Tipranavir, a PI being developed by Boehringer Ingelheim, is currently in Phase III studies and, when boosted by ritonavir, is active against HIV strains that are resistant to currently available PIs. However, the actual utility of tipranavir in some salvage patients with several (3 or more) major PI-resistance mutations is limited without additional effective agents in the regimen. Tibotec has 2 agents in the pipeline, TMC114 and TMC125, a PI and an NNRTI, respectively. Both agents appear to have activity against drug-resistant viruses and are being studied in Phase II trials. Potentially, both agents could be investigated in combination in the same study sample.

Entry inhibitors in the pipeline

In addition to the agents already described, new classes of drugs are also being developed. These include different types of entry inhibitors (see Table 2) that may affect various steps or sites in the entry process (ie, attachment, fusion, or entry), such as the CCR5 ("R5") and CXCR4 ("X4") coreceptor antagonists being developed by several companies or the monoclonal CD4 antibody being investigated by Tanox, a small company in Houston. George Hanna, MD, from Bristol-Myers Squibb, commented that *in vitro* testing has demonstrated synergy between different kinds of entry inhibitors, potentially creating a new HAART regimen for patients who have exhausted the traditional options. While the development of any new class of antiretrovirals can only benefit the HIV-infected population, these advances come with their own sets of challenges. Dr. Ogden discussed how inhibition of a human protein such as CCR5 may not necessarily have the same result as the deletion of that protein, such as in patients with the homozygous Δ32 CCR5 mutation. Likewise, these new drugs may require specific assays that are currently unavailable. In particular, before

Table 2. HIV entry inhibitors in clinical development

Drug Name	Mechanism of Action	Phase of Development	Company
AMD-070*	CXCR4 coreceptor antagonist	Phase 1	Anormed
AMD-887*	CCR5 coreceptor antagonist	Phase 1	Anormed
PRO-140†	CCR5 coreceptor antagonist	Phase 1	Progenics
BMS-488043*	Attachment inhibitor	Phase 1	Bristol-Myers Squibb
UK 427,857*	CCR5 antagonist	Phase 1-2	Pfizer
SP-01A*	Entry inhibitor (specific mechanism not yet defined)	Phase 1-2	Samaritan Pharmaceuticals
SCH-D*	CCR5 coreceptor antagonist	Phase 2 (early)	Schering Plough
TNX-355†	Attachment inhibitor (CD4-binding)	Phase 2 (early)	Tanox
GSK(GW)-873140*	CCR5 coreceptor antagonist	Phase 2	GlaxoSmithKline
PRO-542†	Attachment inhibitor (CD4-mimicking)	Phase 2	Progenics

Source (with some modifications): *2004 Antiviral Pipeline*, by Rob Camp, prepared for Treatment Action Group.
aidsinfonyc.org/tag/tx/pipeline2004.html
*orally bioavailable
†currently administered by injection or infusion

using the coreceptor antagonists, the significance of a patient's predominant viral population/tropism (R5 or X4 or mixed) must be assessed. How such information will affect patient access remains unclear, as does whether or not highly treatment-experienced patients, particularly those with mixed or dual tropic (R5/X4) virus, will benefit from the coreceptor antagonists in the absence of other effective drugs. Moreover, there is a potential risk of accelerating disease progression if a patient's virus switches from R5- to X4-tropic virus.

NEXT STEPS AND RECOMMENDATIONS

Much of the meeting focused on suggestions for what could be done to improve the landscape of salvage therapy from 2004 forward. Participants agreed that routine resistance testing would be advantageous in this patient population. Indeed, Stanley Lewis, MD, a general internist at The University of Texas Health Science Center at Houston, pointed out a common misperception among patients and even some providers: that prior exposure to an antiretroviral agent (even with an absence of detectable viremia) excludes future use of that agent because of drug resistance. The adoption of resistance testing as a standard of patient care and in clinical trials is of particular use in salvage for guiding treatment decisions, establishing OBT, etc.

Dr. Deeks reviewed ongoing studies of patients with MDR virus. He described several strategies used to balance adverse effects, regimen complexity, and clinical efficacy. He noted that some patients seem to sustain immunologic responses with simplified regimens. In particular, patients maintain immunologic benefits despite discontinuing protease inhibitors and staying on only NRTIs (see Figure 2). The benefit of continued NRTIs seems to result from decreased viral replicative capacity. The utility of the replicative capacity (RC) assay, which is being offered along with some resistance tests, was also discussed, though the clinical significance of this assay has yet to be validated.

In addition, the utility of TDM was also considered as a tool to help suppress virus and manage drug toxicity. In Europe, performing TDM in salvage patients is standard clinical practice and is actually supported by the drug manufacturers. However, in

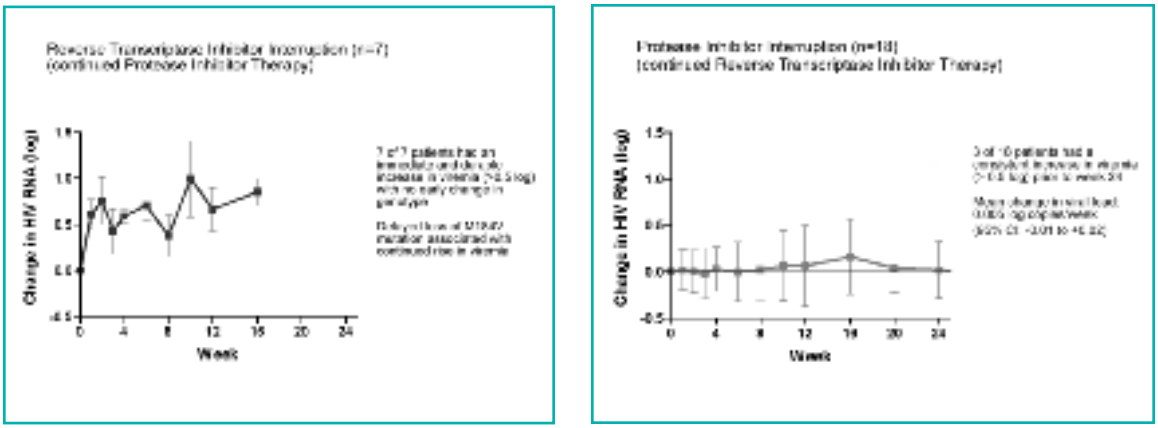

Figure 2. **Data from pilot studies in salvage patients being followed by Steven Deeks and colleagues**

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the US, routine TDM is only performed in certain patients, including pediatric patients, pregnant patients, patients with HCV co-infection, and those patients taking a concomitant drug known to interact with antiretrovirals. Though it could benefit the drug development process, Courtney Fletcher, PharmD, of the University of Colorado Health Sciences Center, explained that TDM is not used in the US to facilitate the drug development process. Drawbacks of TDM are its expense, limited assay availability (and no availability for some antiretrovirals), confusion over interpretation of results, lack of studies demonstrating widespread applicability, and the absence of any well-standardized, commercially-available assay to monitor drug levels. One debate centered on cost versus benefit of routine TDM, and some meeting participants questioned how many patients would actually benefit from this type of testing.

The risk of repeatedly failing regimens and potentially eliminating the benefit of new drugs is a common reason why physicians do not want to enroll their salvage patients in some randomized clinical trials for fear of rapidly using up all available options. While randomized, controlled studies are imperative to answering questions regarding drug efficacy, they should not be answered at the expense of the patients in the control arm. Consider, for example, the patient who is naïve to T-20 and who has high levels of resistance to all available NRTIs, NNRTIs, and PIs. If such a patient enrolls in a study of a new agent plus optimized background (which would often include T-20), then randomization of that patient to the control arm will result in the patient being essentially treated with T-20 monotherapy.

Typically, studies show differences between the control arm and investigational arm quickly. Thus, one solution proposed by Dr. Cohen was to allow patients in the control arm to receive the investigational agent once activity has been demonstrated (prior to 8 weeks). This "staggered" approach may allow patients to benefit before any T-20 resistance develops. An inherent limitation of this approach is the lack of long-term safety comparison data between the 2 patient groups. However, Kimberly Struble, PharmD, of the FDA put these concerns to rest and explained that drug approval is granted based on the entire package submitted by the company, which will contain long-term safety comparison data in less-experienced patients. Nevertheless, Dr. Deeks felt this staggered approach was not practical given the fact that resistance to T-20 often emerges rapidly in the presence of incomplete viral suppression.

An alternative salvage therapy study design suggested by Dr. Deeks was to randomly assign treatment-experienced patients (who are naïve to T-20) to receive OBT + immediate T-20 + new agent or OBT + delayed T-20 + delayed new agent. Data collected from the TORO studies could be used for comparison purposes to define *a priori* what kind of response would be needed to prove that the new agent was effective and potentially avoid jeopardizing a patient's chance of responding to T-20. The precise antiretroviral activity of the agent could be defined in concurrent studies of patients who are treatment naïve or who are minimally pre-treated, an approach the FDA authorizes. The goal of the Phase III, randomized, clinical trial in the salvage setting would largely be to establish safety and to provide an estimate of the drug's activity. Obviously, conducting multi-agent studies with this approach would require additional considerations.

Some potential and often overlooked strategies were proposed by the FDA that could be implemented to help better design studies involving salvage patients: to collect real-time PK data, to dose-

adjust in a small cohort of patients before enrolling a larger cohort, and to use population PK to aid in these dosage studies. Another recommendation was to conduct preliminary PK studies in seronegative volunteers. Dr. Kuritzkes explained that obtaining approval with studies conducted in treatment-naïve patients may allow researchers to have more flexibility in designing studies for the salvage population because industry would not have the pressure of obtaining approval at that point. However, this strategy still introduces a delay in bringing new and effective agents to the salvage patient. Others pointed out that small pilot studies, even case studies of single patients, are still helpful and can provide important information on drug activity, safety, PK, and interactions. A suggestion was made that researchers submit concept sheets to industry to conduct these small studies. In terms of study endpoints, advocates suggested that measures like quality of life, a reasonably healthy immune system, and a lower (but not undetectable) viral load would be more appropriate endpoints for this type of patient.

During the meeting, Dr. Ogden reviewed specific goals of the drug development process in the salvage setting. These included minimizing toxicities, treatment cost, pill count, and dosing frequency; developing drugs with activity against resistant viral strains; discovering drugs that improve antiretroviral drug levels without increasing toxicities (eg, CYP3A4 inhibitors like ritonavir); finding new molecular therapeutic targets; and studying multiple investigational agents in combination. One strategy proposed by Dr. Fletcher was to "learn in a small population and confirm in a large population." This approach may provide a means to answer some of these prevailing questions.

The need for multi-experimental agent trials with cooperation from multiple pharmaceutical companies was discussed at length throughout the meeting. One recommendation appreciated by all was to hold a meeting between the FDA and regulatory representatives from the pharmaceutical companies so the FDA could address the regulatory representatives' concerns and emphasize the feasibility of multi-drug/multi-company clinical trials. Dr. Murray explained that the FDA could provide certain incentives to pharmaceutical companies developing drugs for this patient population such as accelerated approval, priority review, and fast-track status. Government networks and cohorts, such as the ACTG and CPCRA, may be the best chance for the salvage community because such research networks have the ability and wherewithal to conduct these types of trials. Indeed, Dr. Gulick emphasized that a top goal of these networks was the development of more effective treatments for highly treatment-experienced patients. Eric Lefebvre, MD, from Tibotec acknowledged that his company was considering this type of design for studies investigating TMC114 and TMC125, which are currently in the same phase of development at Tibotec.

Representatives from several community advocacy organizations emphasized the need for HIV researchers and pharmaceutical companies to think "outside the box" and questioned if the HIV community was at a point of diminishing return in terms of the types of antiretroviral drugs being developed. Indeed, will the approval of 5 more PIs have a considerable impact on the HIV-positive community? Throughout the meeting, advocates called on the pharmaceutical companies to collaborate in studying multiple agents in combination so that salvage patients could benefit. Another challenge in treating HIV-infected patients is diminished immune system function, even in the presence of a suppressed viral load. Incorporation of immune-based therapies, such as interleukin-2 and therapeutic vaccines, may ameliorate this situation and keep patients healthier, thus allowing them to benefit even more from available antiretrovirals drugs. The question of why humans get AIDS when other primate species do not was also raised, and some participants felt

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that exploration of this discrepancy could provide some answers on how to battle this virus. In addition, the important role of advocacy organizations was emphasized in the continued education of patients on topics such as the benefits of a healthy lifestyle and medication adherence.

Finally, another issue identified was barriers (waiting time, paperwork, etc.) to expanded access and compassionate use when patients have no other options. One solution proposed by Veronica Miller, PhD, the executive director of the Forum for Collaborative HIV Research, was a 2-stage strategy whereby a drug is released for compassionate use after the drug has been studied for a short time (12 or 16 weeks) and then subjected to a wider expanded access after 24 weeks of study. Mike Youle, MD, an HIV-treating physician from the Royal Free Hospital in London, commented that tipranavir was distributed in a similar manner in the United Kingdom. Another solution might be to provide additional funding to clinics to run these types of programs. Unfortunately, in light of the recent funding cutbacks, this recommendation may not be realistic.

CONCLUSION: THE EVOLVING SALVAGE POPULATION

Further complicating any definition of salvage is that the salvage population itself is evolving. For example, Dr. Kuritzkes explained that patients on salvage therapy today are perhaps quite different from those who are just starting salvage therapy now and in the near future. Earlier salvage patients began NRTI mono-or dual therapy in the 1980s or 1990s. As a result of the inadequate potency of these regimens, they first developed NRTI resistance. When protease inhibitors became available, early use was not always coupled with effective NRTI backbones, such that patients are now battling MDR virus. Today's patients who initiated and failed effective combination therapy will be different in terms of the resistance profiles and treatment requirements. Indeed, Dr. Youle commented that half of the salvage patients he sees today in London initiated therapy after 1999, well into the "HAART era."

But other factors also complicate matters. First and foremost, MDR virus is increasing in the US, with drug resistance concentrated in groups less likely to adhere to complex regimens (eg, patients with psychiatric or substance abuse co-morbidities). In addition, issues such as ease of administration and regimen "forgiveness" (ie, the number of doses that can be missed without developing resistance) may be more important in the future. The introduction of entry inhibitors further changes this scenario.

So, what does the future hold for all HIV-positive patients? Will tomorrow's salvage patients fare better or worse than salvage patients today? Dr. Kuritzkes emphasized the need for collecting data on these patients. As one AIDS activist proclaimed among discussions of clinical trial logistics and appropriate study endpoints, researchers must stay focused on the ultimate goal—curing the devastating epidemic.

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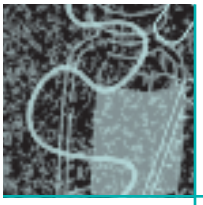

Integration of salvage research into existing networks and structures

(A personal take on Panel 1. Discussion leader: Daniel Kuritzkes)

By David Evans

Panel 1 focused on ways to integrate salvage therapy research into existing networks and structures including government-sponsored clinical trials networks, observational cohorts, and industry-sponsored trials. Though the panel discussed a number of environments in which salvage research is hindered, it concluded that a solution to most of the obstacles must involve greater communication between all stakeholders at much earlier stages in the drug development process.

Dr. Kuritzkes laid out 3 primary areas of focus for the group, all of which demand greater collaboration between industry, the Food and Drug Administration (FDA), academic researchers, and activists:

- To better integrate salvage research into the drug approval process and registration trials;
- To explore new drugs in combination earlier in the development process—even when the drugs are produced by different companies; and,
- To identify ways for Expanded Access (EA) programs to collect more meaningful data without limiting access to treatment or overburdening physicians who participate in EA programs.

Regarding new drug development, industry representatives expressed those concerns most companies have about doing any type of research that could jeopardize their chances for FDA approval. In cases where a company hoped to gain approval for first-line therapy, this often led them to delay critical pharmacokinetic and drug interaction studies that would allow salvage trials to move forward earlier in the drug development process. Industry representatives also noted that because the clinical research staff at the largest companies are so internally focused on attaining drug approval, they do not often interact with community or academia early enough to fully understand the needs and considerations of people living with HIV until well after plans are underway.

However, some in the activist community suspect that industry researchers believe they are already sensitive to such concerns and are conducting the appropriate types of research. In addition, activists suspect these representatives meet with the community largely as a courtesy and because they consider it politically necessary. Getting input "after the fact" is largely a choice they make rather than an accident.

Activists encounter the results of this poor communication constantly. They are asked to give feedback about the plans for a clinical trial only to discover that the company has already submitted the trial design to the FDA and researchers, thereby ensuring that critical suggestions cannot be incorporated. Likewise, companies will claim that they cannot make certain changes because the FDA will not allow them, but when contacted by activists, the FDA claims otherwise, leaving activists in the position of having to decide whom to believe. Early and open communication among all parties would significantly improve this situation.

One researcher suggested that a meeting be held to bring together industry, the FDA, and community (both researchers and activists) to identify areas of common interest that could remove at least some of the obstacles standing in the way of salvage research using new drugs. Most panelists agreed this was a good idea and asked the Forum for Collaborative HIV Research to explore hosting such a meeting. Granted, the issues described during this breakout session have persisted for years despite previous meetings of this type. Nevertheless, pursuing the idea may still be worthwhile.

A particular benefit of such a meeting would be the chance to identify those areas where existing clinical trial networks may be most ideally suited to carry out necessary research. This is particularly critical when studying 2 new drugs produced by different companies. A group formed in the mid-1990s called the Inter-Company Collaborative (ICC) sought to achieve such a goal, but initiated little meaningful research. One major stumbling block the ICC grappled with was anti-trust laws. The panel suggested that the government's clinical trial networks could provide just the kind of neutral playing field necessary to minimize anti-trust concerns. For this to be successful, however, companies would be required to work much more collaboratively with community activists, the FDA, and government researchers to reduce bureaucracy and conflicting priorities. Still, companies are also concerned that the side effects of one drug might become associated with all the drugs used in such trials. This issue leads some companies to fear that such trials run the risk of damaging their chances of approval.

Greater collaboration and coordination could also improve the process by which meaningful data can be collected from EA programs. However, rather than place additional reporting burdens on an already overwhelmed network of community physicians, the panel suggested that large existing cohorts could serve as a model for data collection purposes. Use of EA programs to collect consistent and reliable data could provide earlier safety and drug interaction data and allow companies and researchers to more quickly identify prospective participants for follow-up studies. But this will be impossible to accomplish without resources going directly to the physicians who must collect and report the data.

Greater integration of salvage research into the drug development process will not be easy. The upcoming recompetition of government grants for AIDS research could significantly change existing clinical trials networks. Even changes for the better could delay new salvage research as all parties adapt to new systems and structures. Moreover, the escalating crisis in healthcare and drug access in the US is making treatment of people in salvage situations more difficult. Increasing drug prices combined with shrinking public and private healthcare resources are leading to growing numbers of people living with HIV/AIDS who have neither expert care nor access to new treatments. However, little has been easy in the fight against AIDS, and the panel unanimously agreed that greater communication and collaboration among industry, community, and government is a critical next step to increase and enhance clinical trials for people who have few treatment options.

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Proof of concept studies/translational research; new hypotheses

(A personal take on Panel 2. Discussion leader: Kimberly Struble)

By Bob Huff

So you've developed a new drug that is designed to block HIV at a novel point in its lifecycle. This is not a "me-too" drug but a whole new approach. Your drug is nicely active against HIV in the test tube and didn't raise any worries in tests in mice and dogs, so it's time to move forward. You've gotten your preclinical data together and the Food and Drug Administration (FDA) has agreed to let you try it out in people without HIV to see if there is any overt toxicity. After a few studies in "healthies," you've come up with what you think is the maximum tolerated dose, and you now have some understanding about how quickly your drug is absorbed and eliminated in humans. Yet several years and several million dollars later, one big question remains: will it actually lower viral load in people with HIV?

A "proof of concept" study is needed to answer that crucial question before the drug development process can move forward. But what does that entail? This discussion explored some of the difficult questions that are raised when using a new drug for the first time in patients.

Typically, a proof of concept study for an HIV drug might involve giving the experimental agent as monotherapy for 7 to 14 days to an individual with detectable HIV. Another design is a virtual/functional monotherapy study where the investigational drug is added or substituted for another antiretroviral agent for 7 to 14 days in an individual receiving therapy and with detectable HIV. The viral load drop at the end of that period would be the main endpoint of interest, and the rapidity of the viral load reduction (or the steepness of the slope) could be a secondary indicator of the drug's activity.

But these designs raise some ethical questions that must be carefully considered. The possibility exists that resistance to the entire drug class could develop after exposure to a subtherapeutic dose, especially when it is given as monotherapy. This risk is of particular concern because the FDA would like to see some evidence of dose response from a proof of concept study. Seeing a dose response, where the higher dose produces a greater or steeper drop in viral load, gives reassuring evidence that the drug is really doing something. Yet a volunteer could be harmed if drug resistance were to develop during that short time because the dose received was inadequate. Although establishing a dose response from a proof of concept study is desirable, subtherapeutic doses must be avoided. *In vitro* resistance and pharmacokinetic data can help with appropriate dose selection and duration to minimize the development of resistance from subtherapeutic doses.

Another ethical issue concerns the appropriate type of patient to enroll. Risk:benefit issues are important considerations for early drug development. Some feel a treatment-naïve individual (one who still has a full range of treatment options available) might be taking the least risk; however, others feel that because there are many proven durable treatments available, there is a higher risk for treatment-naïve patients because a treatment may have unexpected toxicities or might allow resistance to

emerge that could confound future therapy choices. If a drug is expected to have activity against multi-drug-resistant virus, then the proof of concept study should determine the activity in the patients mostly likely to use the drug, ie treatment-experienced patients. Because risk:benefit issues may be complex for investigational agents, the use of a data safety monitoring board and early treatment stopping rules can be used in protocols to minimize risk to patients.

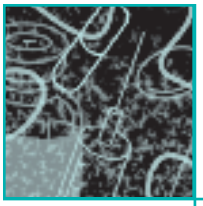
Another issue concerns the expectations of patients after participating in a proof of concept study. Unfortunately, there is no guarantee that someone who has experienced a good response after 14 days can continue to receive the drug after the brief study ends. Several months may be required to evaluate the results of the proof of concept study before a dose is selected and larger trials are begun. Additional drug interaction studies may be required before it is used in combination with other antiretroviral agents. This is especially important for treatment-experienced patients receiving numerous medications, a situation where the risk for drug interactions is large. Also, sometimes a company decides not to continue developing a drug past the proof of concept point. Finally, because so few people have received a drug at this stage of development, vigilance for adverse events must remain high—even after the 14-day exposure has ended. One salvage-related issue for investigators to consider is that highly treatment-experienced patients may be more vulnerable to adverse events than treatment-naïve patients. Obviously, drug development at this stage is not for the faint of heart.

Although small numbers of patients are involved at this stage of drug development, there are significant concerns associated with exposing salvage patients to a potentially useful, albeit investigational, therapeutic agent. For one, exposure to suboptimal doses of a single agent might allow resistance to develop, thus eliminating any hope of using the agent in future therapy. Secondly, the agent might not be further available to such patients because it has ceased being developed or because prior exposure becomes a criterion of exclusion in later clinical trials. Third, removing salvage patients from stable therapy—even in the setting of virologic failure—is risky and potentially harmful if not done with the intention of beginning a new, active regimen to resuppress virus.

So how do investigators and patients evaluate the risks versus the benefits of participating in these very early drug trials? As in any trial, this process begins with a thorough discussion of the risks and a commitment to the principle of a patient informed consent. Yet the conduct of these early trials is rarely transparent or obvious to members of the HIV treatment community. Such trials may take place in foreign countries where people have fewer treatment options or may offer paid inducements to participants to accept the risks. This presents additional ethical challenges. But these studies are a necessary step that every trailblazing drug must take. With proof of concept in hand, the investigators can move forward with learning how to get the most out of this latest agent against HIV.

Translational research or new therapeutic approaches are always likely to come with such risks to patients, especially at early but critical stages of development. Patients in salvage situations are often desperate for new therapeutics to treat HIV, and yet their decisions to participate in clinical trials must be made with careful consideration to avoid losing precious options down the road.

Bob Huff is Editor of *Treatment Issues*, a publication of Gay Men's Health Crisis ***(gmhc.org)***.



The future of salvage therapy: monitoring systems for patient outcomes

(A personal take on Panel 3. Discussion leader: Douglas Ward)

By Matt Sharp

In looking to the future of salvage therapy, consideration must be given to what treatment strategies will work best, what the salvage population will look like, what types of patients will be available for trials of new drugs, and what resources will be available to provide the new drugs. Will multi-drug resistance (MDR) of the virus occur with the treatment regimens used today? How can research provide answers for how to circumvent MDR? These were the topics discussed in Panel 3, which focused on ways to define, monitor, and treat the current salvage population and the how the salvage population will prevail over time.

Doug Ward, MD, an HIV-treating physician, defined his salvage population as 2 groups: those who were treated with sequential monotherapy and are typically stable, and those who may be stable yet have MDR. Because of the availability of back-up regimens, Dr. Ward doesn't believe he is creating any new salvage patients today. Panelists noted that it is difficult to determine the actual extent of the salvage population. Are there new salvage patients or just treatment-experienced patients who are stable but have MDR regardless of CD4 T cell count? Also, why are there clinical differences between patients who have similar viral loads? One observation is that today's patients seem to be doing better with lower T cells, and changes in viral pathogenicity may be the reason. Because Dr. Ward's clinic is not representative of the larger HIV-infected community, how can we define this population?

The HIV epidemic in the US itself has changed, affecting many more women and minority populations. In addition, the development (from nonadherence and other factors) and transmission of drug resistance are affecting the epidemic in regions where antiretroviral treatments are widely available, such as the US. To make matters worse, clinical trial enrollment is becoming more challenging, perhaps because of the wide availability of existing treatments or issues of distrust concerning the medical establishment. All of these issues make studying and treating the salvage population as challenging as ever.

Because health clinics may not be completely representative of the salvage population, one way to define the salvage population is to utilize databases from Virologic or other diagnostics companies. These databases contain information on the percentage of people carrying specific resistance patterns, though such databases lack medical history information. However, if the research community can accept the drawbacks, this type of database may be useful for quantitative analysis. Nevertheless, it still comes back to defining the salvage population. Clinical cohorts such as Johns Hopkins, the HIV Out-Patient Study (HOPS), and the University of Alabama may provide some definition of the salvage population, though they may be collecting information on just treatment-experienced patients, therefore skewing their data collection toward patients with more resistance. Little preva-

lence data exist in nonacademic settings to help define a population of salvage patients. One cohort study is being developed. Other data from Mike Youle, an HIV-treating physician attending the Think Tank, also exist from his clinic.

The activist community has been attempting to solicit useful data from expanded access (EA) programs that may provide some information on the salvage population. Again, the caveat is that treatment history information is often not collected in these programs. Extensive sampling technique studies that collect population-representative information may be another way to characterize the salvage population. The Centers for AIDS Research (CFARs) have the CFAR Network of Integrated Clinical Systems (CNICS), which is a large system trying to link existing CFAR site databases electronically, but there are apparently logistical complexities with the linking of sites. While this system can define the population, there is no sampling and no information on medical history. However, there is a denominator of patients, their regimens, and levels of resistance. In any case, it may be the best way we have at this point to assess the salvage population.

Another question is how can we best predict treatment failure? There is concern that quality of life (QOL) assessments in determining treatment failure in the salvage population are not being adequately monitored and evaluated. Much attention has been placed on pharmacokinetics (PK) and efficacy, but is there a standard tool for QOL evaluations that could be adapted for use in clinical trials for drug development? The ACTG uses a QOL assessment tool that is accepted for many clinical trials.

In addition, guidelines on how to treat these patients are still unclear. Is "mega-HAART" (HAART that employs more than 3 drugs, and as many as 6 or 8 drugs, to treat HIV) still a useful strategy for salvage patients? Most panelists agreed there is little evidence to support it. However, if used today, mega-HAART would mean fewer pills since many drugs have been reformulated or coformulated. Have dual-boosted protease inhibitors (PIs) caught on for salvage therapy? An increase in pill burden and potential pharmacologic interactions may be reasons to not use dual-boosted PIs. What about enfuvirtide (Fuzeon or T-20) for those who are treatment experienced but fairly stable with relatively low viral loads and a CD4 T cell count above 200? Consideration must be given to save future options in this population and to avoid using novel therapies like T-20 too early, as it may be more useful in a deeper salvage setting. Intermittent therapy and regularly switching regimens may become promising approaches as more drugs are developed from new classes. Also, there may be utility in alternating Kaletra monotherapy in such a setting, given recent promising data. Further, would the use of an intermittent strategy be beneficial in patients who start therapy early and gain viral control?

Newer drugs are selecting for different types of resistance, especially in nucleoside reverse transcriptase inhibitors (NRTIs), so that there may not be large numbers of thymidine analog mutations (TAMs) developing in patients who have started therapy in recent years. This changes the treatment paradigm and the expectations for new drugs. We know about "type 2" or "second generation" nucleosides, such as abacavir (Ziagen) or lamivudine (Epivir), which are distinguished by the 184 codon susceptibility. So, there needs to be newer compounds in the older thymidine analog nucleoside generation—drugs such as Retrovir (zidovudine or AZT) and Zerit (stavudine or d4T)—without the toxicities, which should be considered for any new drugs being developed. Some panel members ques-

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tioned whether this would be applicable over time depending on growing mutation patterns and the variability of viruses with the 65 or 184 mutations. Other questions persist with newer drugs; for example, whether tenofovir (Viread) is clinically effective in those who are highly treatment experienced and for whom it is the only phenotypically susceptible NRTI.

Is there additional benefit for use of phenotypic testing in MDR patients? This type of testing may be useful depending on the patient. Phenotypic testing provides a benefit when there is some susceptibility to antiretroviral drugs. Questions still exist concerning cost effectiveness and where the use of phenotype and genotype tests is most practical. A replicative capacity (RC) assay is currently done with a commercially available phenotype test, and there is pressure to explore the idea of requiring a separate payment for RC tests. Obviously, the clinical utility of such a test should first be established through more studies in large numbers of patients.

One of the biggest salvage research questions today is where would the therapeutic drug monitoring (TDM) test be most useful in the salvage paradigm? Such testing is used widely in Europe. The panelists agreed that TDM results are much simpler to read than those of a resistance test. If TDM is being used to choose drugs for patients with multi-PI resistance, then population-based information on PK and protein binding for the particular drug being tested should be considered. However, drug PK reports are not updated, especially in the current era of boosted PIs. Also, TDM cannot be used for nucleosides because of their intracellular activity (blood plasma levels may not accurately be a reflection of drug penetration and therapeutic activity). Therefore, the use of TDM will be best for determining therapeutic doses for individual patients or in patients with hepatitis co-infection to look for liver toxicities.

In summary, resource allocation and access to drugs will continue to be an issue for patients in salvage situations. One panel participant suggested that the problem was the overall structure of the healthcare system. At present, this is especially problematic for indigent patients who cannot access specialty care. Such situations actually create salvage patients. Recent studies have shown that adherence is actually improving in salvage patients, so treatment failure may get worse but resistance data may improve. Some consider it far worse to be highly resistant to a bad regimen than nonadherent to a good regimen. As far as treatment guidelines are concerned, the pendulum may swing in the direction of starting antiretrovirals earlier as regimens become easier to take and have less toxicity. Starting treatment early may be advantageous for several reasons. While no one is advocating that patients be on therapy for the rest of their lives, a brief period of early therapy may be beneficial. Some believe that patients are easier to treat overall if they start therapy earlier. With more research, time will tell if this is true.

Matt Sharp is a person living with AIDS and is Director of Treatment Education with Test Positive Aware Network in Chicago (***tpan.com***).

Regulatory issues and challenges in salvage therapy

(A personal take on Panel 4. Discussion leader: Trip Gulick)

By Martin Delaney

Panel 4 focused on how regulatory issues were presently affecting options for salvage patients. Initial discussion noted that the numerous changes and improvements made at the Food and Drug Administration (FDA) over the last 20 years, often as a result of community input and pressure, have eliminated most of the regulatory obstacles that once existed. In short, today the FDA is not perceived as a major roadblock to the development of salvage therapy.

Nevertheless, the participants of the group pointed out that this did not mean that people requiring true salvage therapy could always get what they needed. One of the biggest problems in the realm of salvage therapy is that it is seldom possible to obtain access to more than one new drug at any particular time. Yet we know that simply bringing in one effective drug, when a person is failing all available drugs and combinations, provides little more than short-term improvement. The addition of a single new drug in a salvage setting is basically equivalent to monotherapy and, with the drugs presently available, it is all but impossible to achieve a lasting and powerful antiviral response with a single drug. The necessity of effective combination therapy is even more critical in the salvage setting than it is for people initiating antiretroviral therapy.

Some of the clinicians in the discussion group commented that even "failing" drugs often provide a degree of viral suppression. One reason for this is that the drug-resistance mutations that develop and cause a drug to "fail" also may cause it to replicate less effectively. New diagnostic tests that measure the replicative capacity of a person's virus are currently being studied to help quantify and characterize this effect. Nonetheless, the most desirable situation is for the person in a salvage situation to have access to at least 2 new active drugs at the same time.

Several obstacles make this scenario difficult to achieve. One major factor is that multiple new drugs rarely, if ever, come from the same company. If a single company is developing 2 antiretroviral agents, they are usually not in the same stage of development because each drug moves forward at its own pace. Although different companies have historically shown little or no willingness to make their individual drugs available under a common timeline, the FDA has stated that it does not oppose study designs that include 2 or more investigational new drugs. Community pressure regarding these issues therefore needs to be directed, not at the FDA, but at the individual companies developing the drugs.

For example, Tibotec has 2 drugs in parallel development, a protease inhibitor (PI) with good activity against PI-resistant virus and a new non-nucleoside reverse transcriptase inhibitor (NNRTI) that over-

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comes viral resistance to other drugs of this type. Both community advocates and scientists agreed that the situation developing at Tibotec was especially well suited to test an approach studying 2 investigational agents in one study. Developing clinical trials that allow people access to these 2 new drugs at the same time should be relatively simple. In addition, tipranavir, a protease inhibitor developed by Boehringer Ingelheim, will be also accessible in this time frame. Farther down the road, at least 2 new entry inhibitor drugs will most likely become available at a similar time. Thus, the prospects for treating people in need of salvage therapy with 2 or more new drugs at the same time appear quite good.

This issue of multi-drug availability also pertains to expanded access (EA) programs. Almost every drug has an EA program that makes the drug available to people in need before formal FDA approval. The challenge for salvage therapy is to coordinate 2 or more such programs so that salvage patients have access to 2 or more new drugs at the same time. Again, this issue is not so much a regulatory issue as it is a "collaboration" issue between pharmaceutical companies. Community pressure must be placed on the individual companies to coordinate their EA programs. While such coordination may be challenging, there is no inherent reason why this cannot be achieved.

Some advocacy representatives commented that even if EA programs could be coordinated, and some studies combined 2 or more new drugs, there would still be patients who could not obtain access to multiple new agents at the same time. Not all people are qualified for these clinical trials, nor do they all live in locations served by the trials. Furthermore, there will always be people who need access to multiple new drugs prior to the launch of EA programs. This highlights the dilemma of a number of people in the salvage setting and asks the question "how can we provide these patients with the necessary access to multiple new drugs at the same time?"

At the Salvage Therapy meeting, researchers and community activists alike found this to be the most challenging situation. Fortunately, this dilemma is not that common. One possible approach is the use of a mechanism that would provide access to the needed new drugs on a "case by case" basis (sometimes called "compassionate use"). Some of the clinicians, however, feared it would require a great deal of paperwork on their part for each patient. In response, community advocates pointed out that the monumental paperwork procedures were not necessarily required and instead a bad habit of the FDA and pharmaceutical companies. Individual access should be achievable with minimal paperwork as long as the manufacturers and the FDA are committed to making it happen.

Martin Delaney is the founder of Project Inform (***projectinform.org***).

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