

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 treatment-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 pharma-

ceutical companies, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the European Medicines Agency (EMA). 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 univer-

sal 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.

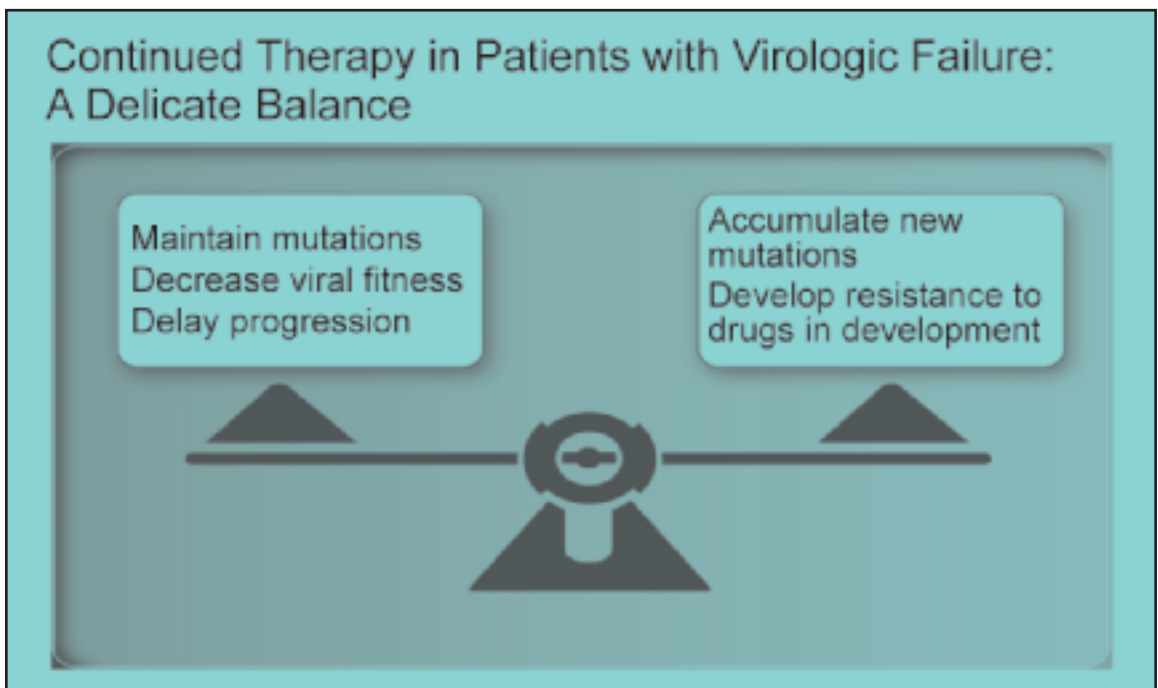


Figure 1. The challenges of continued treatment in salvage patients as presented by Joel Gallant

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 *RITA!* 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 popula-

tion 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 anti-retroviral 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 $\Delta 32$ 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 resis-

tance. 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

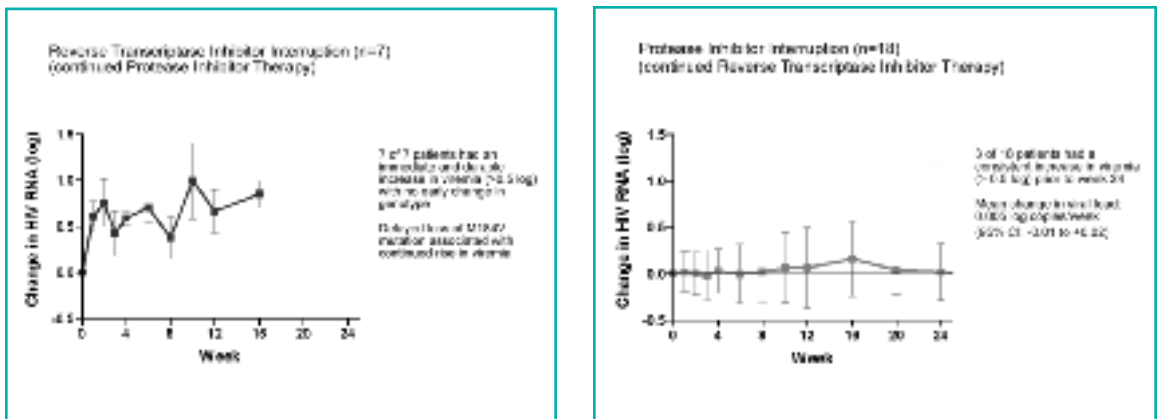


Figure 2. Data from pilot studies in salvage patients being followed by Steven Deeks and colleagues

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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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