

NEW MEDICATIONS, SALVAGE THERAPY AND TREATMENT STRATEGY

A TREATMENT MANUAL FOR HIV INFECTED PATIENTS WITH DRUG RESISTANCE

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Introduction to treatment of drug-resistant HIV

This manual reports with great enthusiasm and hope that new antiviral medications just becoming available will finally enable doctors to achieve a long dreamed of goal to successfully treat almost every single HIV infected patient. This includes patients who were previously very difficult to treat due to extensive drug resistance.

This manual endeavors to show how these new medications can be optimally used to achieve the best outcomes for patients. It discusses

1. How to use newly available potent antiviral medications like the Merck Integrase inhibitor called raltegravir, Pfizer CCR5 receptor inhibitor called Maraviroc, and Tibotec non-nucleoside TMC125 along with other recently available as well as older medications.

2. How to achieve important treatment goals such as an undetectable viral load and avoiding new drug resistance by using these new medications in properly formulated combination therapy regimens.

3. How to strategically individualize treatment by showing how basic principles of treatment should be used. These well accepted principles listed below will be discussed in detail and then illustrations given

regarding how to strategically use them to achieve the best chance of excellent results. These principles of therapy are:

- a) drug potency
- b) drug resistance
- c) combination therapy
- d) drug toxicity
- e) drug dosing and drug interactions
- f) drug adherence issues
- g) drug access and cost issues

All of the above principles need to be considered before a clinician prescribes a new regimen for a patient.

4. This manual also discusses how to treat healthier, often easier to treat patients with drug resistance using these basic principles of treatment. This includes the large group of patients usually with T helper cells greater than 200 who often maintain stable and/or increasing CD4 cell counts even when drug resistance to some of the meds they are taking occurs.

New and evolving knowledge about the way drug resistant virus interacts with the immune system suggests that three additional principles of treatment should be considered in formulating treatment regimens for healthier and easier to treat patients.

- h) viral fitness (often favorably reduced in patients with drug resistance)
- i) immune activation (often favorably diminished in patients with drug resistance)
- j) HIV specific immunity (often favorably increased in patients with drug resistance)

5. This manual examines the possibility that for some healthier and easier to treat patients with drug resistance a careful consideration of the principles of therapy may suggest treatment goals of maintaining low but not necessarily undetectable viral loads.

This strategic approach may avoid serious but potentially unnecessary drug toxicity that might occur with a maximally suppressive regimen in some patients and at the same time preserve future treatment options.

6. This manual hypothesizes that some patients with drug resistance may actually be getting easier to treat over time.

If so, there may be an Alternative Pathway of treatment for some patients enabling those patients to evolve to less treatment and less toxic treatment without necessarily achieving the goal of maximal virus suppression.

Simply put, as patients become easier to treat they may need less antiretroviral therapy.

Changes in immune activation, viral fitness and HIV specific immunity in some patients who develop drug resistance may account for the success of this pathway.

More clinical and basic science research is needed to better characterize and understand this important group of patients.

7. Please note nothing, absolutely nothing in this treatment manual should be construed as specific treatment advice. Individual treatment decisions should be made on an individualized basis within a close doctor patient relationship. In addition, excellent sources of treatment information like the Department of Health and Human Services Guidelines for HIV Treatment, salvagetherapies.org, Aidsmap.com, poz.com, aidsmeds.com, HIVandhepatitis.com (all sources I consult) among many other excellent sources should

be resourced.

I have hoped to add my knowledge and insight from twenty plus years as an HIV clinician in a way that might complement these excellent sources.

Salvage therapy: Why new medications are needed to treat multi-drug resistant HIV (MDR HIV)

The treatment of patients with resistance to the three most commonly used and widely available classes of medications is called "salvage therapy". Recently, a Wall Street Journal article on this subject reported that 40,000 Americans living with HIV have significant amounts of drug resistance and are in need of better therapies [1].

This sobering article reported that despite the extraordinary progress made in treatment over the past decade due to the availability of HAART that the mortality rate of HIV infected patients in 2005 was 40% of what it was in 1995, the year prior to the beginning of HAART.

Although it is not clear what percentage of those patients died fully or in part because of difficult to treat drug resistant viruses I was surprised by the high death rate. Nelson Vergel, a well known and pioneering treatment activist, stated his belief in the same Wall Street Journal article that the large population of HIV infected patients struggling to survive with difficult to treat viruses and in need of better salvage therapy were the new "invisibles". He points out that "they are usually too sick or tired to advocate for their rights to access investigational drugs that may save their lives".

Sadly, I agree with Nelson's assessment. The needs of these patients have not been given the proper attention that they deserve to be by the pharmaceutical companies and Key Opinion Leaders (KOLS) within the HIV medical profession who influence medical practice and research. [Key Opinion Leaders are generally well regarded experts in medicine who are also courted and paid by drug companies to help market drugs to the public and to the medical profession]. Potentially important new drugs have been halted in development. Other promising treatment approaches that do not provide potential for a big pharmaceutical company to cash in have been ignored.

I believe that the new or shortly upcoming availability of these new drugs should dramatically reduce the high mortality rate still seen in the HIV infected population. The intention of this essay is to discuss both in general how we in the medical profession could do better in improving the quality and relevance of medical research and explain how I believe the new medications can be used to optimize and individualize our patients' treatment.

Improving outcomes for patients needing salvage therapy with new medications

It's exciting news for HIV infected patients and the clinicians who take care of them that several new antiretroviral drugs are becoming available.

New drugs like Merck and Gilead's integrase inhibitors, Pfizer's CCR5 receptor blocker, and Tibotec's new non-nucleoside reverse transcriptase inhibitors, TMC-125 and TM C-278, hold great promise in helping to successfully treat difficult to treat patients with a lot of prior drug resistance. What is most exciting and unique about this new wave of medications is that it is the first time that several new drugs are becoming available for clinical usage at around the same time since the beginning of Highly Active Anti Retroviral Therapy (HAART) in 1996.

These new drugs work in one of two ways. The first way is to block HIV replication at new and different points of the HIV life cycle than previously available drugs. The second way is to inhibit past targeted points of the HIV life cycle with new structural designs that retain activity even when resistance has developed to similar drugs. Even heavily treated patients with extensive drug resistance should not be resistant to these new drugs.

Thus these new meds can potentially be used as highly active components of a new combination therapy regimen for patients in need of new and better treatment. Later we shall in detail explain why combination therapy regimens usually require at least three fully active drugs whether newer or older to be optimally effective for drug resistant patients. Many patients with multi drug resistant HIV are resistant to most and sometimes all of the older medications.

Previously, drugs that had potential activity for drug resistant patients were made available just one at a time. This meant that when patients who needed new and better therapies tried new drugs there were often not enough active drugs to combine the new drug with to result in a sustained response to the new regimen.

But today for the first time many multi-drug resistant patients have a chance to start three new fully active drugs at the same time. This exciting and important development means that patients who are in need of better therapies have a real chance of getting a full response to a new regimen that includes several new active drugs.

As of August 2007, the Merck integrase inhibitor, Tibotec's TMC 125, a non nucleoside reverse transcriptase inhibitor, and Maraviroc, a CCR5 inhibitor made by Pfizer, are available in expanded access programs. Expanded access programs are designed to make available new medications to patients who urgently need them while they are still being tested in clinical research prior to F.D.A. approval.

In addition, there are several protease inhibitors, in particular Prezista and Aptivus that have been FDA approved in the past 3 years and are usually active in patients even with extensive protease resistance.

However, the availability of new medications by no means guarantees therapeutic success and I believe that a careful strategic application of time-tested principles of therapy is essential. Doctors and patients should set realistic goals and use new meds strategically and effectively instead of wasting their potential.

How many new or active drugs are needed to treat MDR-HIV?

Most patients who are currently in the predicament of not having enough new active drugs to compose a fully effective and sustainable regimen have historically been treated sequentially with one or two new drugs at a time. Unfortunately, three fully active drugs are usually needed to dramatically increase the likelihood of success in a salvage therapy combination.

Unfortunately, for many patients with drug resistance three fully active drugs were not available at times of need and as new drugs continued to become available those drugs were introduced one or two at a time to these patients. Consequently, these patients continued to develop drug resistance to each new drug they tried.

For example, many patients treated for the first time with protease inhibitors when Highly Active Antiretroviral Therapy known popularly as HAART first became available in 1996 were already treatment-experienced with the available class of meds, the nucleoside reverse transcriptase inhibitors (NRTI'S - AZT, 3TC, DDI, DDC, D4T). This group of patients was usually already resistant to NRTI'S. Patients who had never taken NRTI'S before and were simultaneously started on NRTI'S and proteases did much better than patients that were already nucleoside-experienced who initiated new protease drugs with NRTIS to which they were already resistant. .

Similarly, when Fuzeon (T20) a novel and highly potent drug with a unique mechanism of action first became available in 2003 the patients who needed it most (highly treatment experienced patients with low T helper cells and high viral loads and multi drug resistance) were least likely to durably benefit from it due to the lack of other active agents to combine in with. The same thing could be said about Aptivus two years later.

The Challenges Inherent in New Meds

Of great importance is that now there is the potential for even the most drug resistant patients to benefit from new salvage therapy regimens. This includes patients who may have tried Fuzeon and or Prezista or Atrivus and developed resistance to these drugs. In fact there is the potential for patients with multi drug resistance who are quite advanced and may be ill to make extraordinary recoveries with salvage regimens based upon these new meds.

However, given the newness of these meds and the inherent challenges in treating highly treatment experienced and drug resistant patients it is important to examine how to make best use of these new HIV meds. Little clinical experience is available to even the most experienced of clinicians in the optimal usage of new drugs like raltegravir (Merck's integrase inhibitor), TMC-125 or Pfizer's Maraviroc. I believe the best way forward is to carefully apply principles of therapy that have evolved out of clinical practice and clinical research focused on achieving realistic goals for therapy.

What principles of therapy are and how to use them to make sure a new regimen is effective

What I call principles of therapy are the considerations that have to be taken into account in optimizing and individualizing each patient's treatment regimen. When I prescribe ARV (antiretroviral) medications to my patients these are the things or principles I take into account in making specific recommendations. Proper prescribing both includes a consideration of each principle independently and how these principles interact in individual patients.

Well -accepted principles of therapy include recognition of the importance of

I. DRUG POTENCY-

When I formulate a new ARV regimen for an advanced drug resistant patient I want to make sure if possible that the combined potency of the regimen is enough to maximally and durably suppress HIV. My goal is for the new combination regimen to suppress HIV replication to a low enough level that my patient's virus cannot replicate sufficiently to develop new resistance to the regimen and undermine its efficacy. That generally means an undetectable viral load (under 50 copies per ml).

If the patient's viral replication is not maximally suppressed then the patient's virus will likely acquire resistance mutations that will reduce the anti viral potency of the new medications. In some highly drug resistant patients, their new regimen may represent their best and perhaps last chance of effective treatment so I want to get the regimen right.

When drugs lack sufficient potency, treatments may fail

For example, what happens if Fuzeon to a patient's regimen without enough independently active drugs to combine with Fuzeon? In this example, the combined potency of the regimen will not be enough to suppress the patient's viral replication to an undetectable level. Consequently, ongoing viral replication will lead to the patient's virus acquiring new mutations that confer resistance to Fuzeon. When resistance to Fuzeon emerges the cost may be the failure of the new regimen plus potentially using up a Fuzeon as a potential component of a future combination therapy regimen.

To complicate matters further, the potency of the proposed regimen needs to be assessed in the context of the level of the patient's viral replication. Patients with higher viral loads may need more potent regimens to increase their chance of success.

Why drug potency considerations are particularly important to advanced patients

When HAART was first applied with the newly available protease inhibitors in 1996, many advanced patients with less than 100 CD4 cells/mm³ or less than 50 CD4 cells/mm³ who were unable to achieve or sustain undetectable viral loads had poor outcomes. In these patients preexisting experience and resistance to the then available NRTIS meant that when the protease inhibitors were added there were

not active enough drugs to combine the protease inhibitors with and patients with this treatment history were unlikely to achieve and sustain undetectable viral loads. Viral resistance developed to the protease inhibitors due to ongoing viral replication and tragically for some patients short term immune and clinical improvements were wiped out, leaving those patients without new effective treatment options.

Very advanced patients today, with less than 100 or 50 CD4 cells are in a similar predicament to those early HAART patients. When we use new medications or new classes of meds like integrase inhibitors it is essential that we carefully assess and maximize the potency of the regimen to give the patient the best chance of achieving and sustaining an undetectable viral load.

It is important to note that healthier patients with higher CD4 counts usually have a different and better outcome when viral rebound occurs and new drug resistance develops. Fortunately, many healthier patients continue to do well for long periods of time even with viral resistance and rebound which does not automatically or even usually translate into immune decline.

It is believed that in many patients on antiretroviral therapy that the same mutations that help the patient's virus to replicate successfully in spite of the presence of HIV meds also weaken the virus's ability to replicate in general. For the past several years there has been an experimental test called a viral fitness test that can measure changes in a patient's virus's ability to replicate as that virus acquires resistance mutations. By this and other possible mechanisms we shall talk about later some patients on treatment continue to do well even when standard tests for resistance suggest that the drugs that they are taking are not active due to drug resistance mutations.

In my opinion some of the clinical leadership in HIV medicine has overly emphasized the risks of drug resistance and urged patients to change treatment whenever some viral rebound occurred. Usually no distinction is made between more advanced patients in whom the consequences of new drug resistance can mean exhausting treatment options and healthier patients in whom new drug resistance may have no demonstrable adverse clinical effect.

I believe healthier patients with drug resistance have different treatment needs and more options than more advanced patients. In healthier ongoing viral replication and even extensive drug resistance does not necessarily call for a treatment strategy focused on sustained maximal viral suppression especially when maximal viral suppression requires more toxic regimens.

II. DRUG RESISTANCE

Drug resistance reduces the potency of drugs to which the patient's virus has developed resistance. A careful assessment of a patient's resistance pattern and treatment history is necessary to help choose the drugs that have the necessary potency that when given in a combination regimen will maximally suppress the patient's virus.

Later in this essay I will suggest a practical model to help achieve this important task.

Drug resistance strategy considerations

Considerations of resistance also include the patient's risk of developing further resistance on their current regimen if treatment is not changed. Continuing a regimen in which ongoing viral replication is taking place and drug resistance is developing could result in the patient's virus acquiring additional resistance mutations.

A number of clinical studies have been published that measure the amount of additional drug resistance that takes place in patients on regimens in which less than maximal viral suppression and ongoing viral replication put patients at risk for additional resistance. In for example the SCOPE study it was found that after one year of treatment with a less than fully suppressive antiviral regimen there was a 44% chance of developing a new mutation

New additional mutations could both further reduce the potency of the drugs the patient is currently taking as well as create cross-resistance to similar drugs that might have useful activity if used before this additional resistance occurred. This, for example may occur with proteases inhibitors in which drug resistance is a often a gradual process. More and more mutations emerge with continued usage of suboptimal regimens resulting in increasing resistance to the whole class of meds.

The Scope Study as well as similar studies have been used to support the notion that the best strategy for a patient on treatment with some viral replication is to change the regimen as soon as possible to a maximally suppressive regimen to prevent the avoidance of additional mutations from emerging that could further limit a patients treatment options. Because the SCOPE study does not measure long -term clinical outcomes and because it is not powered to do so I believe that drawing the conclusion that a strategy of automatic treatment change with the goal of maximal viral suppression is not supported by SCOPE or similar studies.

<http://www.medscape.com/viewarticle/548077>

Not all of the mutations measured as new in the SCOPE trial are of equal clinical significance. For example while it is clear that keeping a patient on a medication in the non-nucleoside class of drugs such as Sustiva or Viramune usually results in a resistance mutation that neutralizes the efficacy of the class of meds, the same cannot be said for keeping a patient on a medication in the nucleoside class or even on a boosted protease inhibitor.

The benefit of a strategy of maximal viral suppression needs to be weighed against its potential costs such as the risk of increased toxicity with new medications, or the strategy not working and the patient developing resistance to new medications or new classes of medications. In addition, as we learn more about the clinical significance of resistance mutations we are finding that some mutations such as nucleoside analogue associated mutations or NAMS may not limit the effectiveness of regimens that include nucleoside analogue drugs. (More on this later)

Resistance does not always mean a treatment needs to be discontinued

Although, the avoidance of higher levels of resistance is often cited as a reason to aggressively change therapies with the goal of maximal viral suppression in my opinion this strategy has been incorrectly elevated to a cardinal principle of therapy. Misapplied it can lead patients be prescribed unnecessarily toxic and difficult to adhere to regimens that have not been shown to improve clinical outcomes in healthier patients.

Patients and clinicians have been unduly pressured to regard some amounts of viral replication and drug resistance as a sign of treatment failure when it fact it is often consistent with an effective treatment meeting realistic clinical goals.

Patients are pressured by pharma sponsored advertising and trade groups to regard achieving an undetectable viral load as the only acceptable outcome of treatment. Physicians are pressured to similarly focus on this end point by pharma sponsored Key Opinion Leaders who tout using all available F. D. A. approved drugs and making frequent treatment changes to achieve this goal that again has not been shown to improve patient outcomes. Heavier usage of more and more expensive drugs clearly benefits pharma.

For example, Clinical Care Options, an online website heavily trafficked by physicians seeking updates, news, and education recently sponsored a teaching case or exercise for physicians focused on how to treat an HIV infected patient with drug resistance. A very well respected and knowledgeable HIV clinician and researcher Dr. Joel Gallant led his colleagues through the case of a patient who continued to develop new resistance to successive regimens due to periods of poor adherence to meds. Interestingly, the patient maintained good and improved T helper counts even when resistance occurred. (More on this shortly)

Participants in the case were given multiple choice options regarding what to do at each point new

resistance developed. The correct answer according to Dr. Gallant was to change the regimen each time viral rebound occurred to maximally re suppress the patient. In the last situation presented in the exercise Dr. Gallant advised a regimen of 7 drugs including Fuzeon in a patient with a viral load of about 500 copies/ml and a T helper cell count of 600. All for a patient who was earlier unable to adhere to a three pill once a day regimen. The costs of this 7drug regimen were not discussed.

I questioned Dr. Gallant about why he was so ardently focused on achieving and sustaining an undetectable viral load in a patient with a high CD4 count. He told me that he believed that drug resistance would eventually lead to treatment failure and an exhaustion of treatment options unless patients were maintained at an undetectable viral load.

Suffice it to say here that the risks of developing additional drug resistance has been exaggerated in some patients when in fact the development of certain resistance patterns may even serve to stabilize the patient and in my own clinical experience help some patients evolve to less toxic regimens. Ironically, Dr Gallant's hypothetical patient may have exhausted treatment options due to unnecessary exposure to new drugs and new classes of drugs.

Many patients with drug resistance are quite stable

It is important to recognize that many patients with drug resistance and even MDR-HIV are clinically stable on their current regimens. Thus it is important to determine if a particular patient is stable and balance the benefits and risks of attempting to achieve an undetectable viral load in a given patient.

Many patients, particularly those patients who started treatment at higher CD4 counts maintain stable or increasing CD4 counts even when viral rebound or resistance occurs. Very early in the HAART era it was incorrectly believed by many that viral rebound due to the development of drug resistance would quickly wipe out whatever CD4 cell improvements that had occurred on treatment. Fortunately, it turns out that when resistance develops viral loads often do not return to the baseline or set point of the patient before ARV treatment. In these patients CD4 cell counts stabilize and sometimes continue to increase for years despite the development of drug resistance.

Viral disconnect - when the immune system stabilizes or improves despite drug resistance

Patients who have this pattern of response to treatment are called "viral disconnect" patients. The term viral disconnect means that the patient's CD4 cell responses to antiviral therapy have become disconnected from the viral load response to therapy. In these patients, the development of drug resistance actually weakens the virus' ability to damage the immune system. Since the maintenance of clinical health depends more on the level of the CD4 count than on the viral load, patients with the viral disconnect tend to do quite well even with detectable viral loads and significant numbers of drug resistance mutations.

Resistance risks were historically exaggerated

Key Opinion Leaders in HIV Medicine considered as experts on drug resistance have made bold and I believe incorrect predictions about how the story of drug resistance would unfold. Some KOLS strongly asserted that every patient, even those at undetectable viral loads, would become resistant eventually to every HIV drug. And since these KOLS also believed that drug resistance would also automatically cause immune decline, they made bold assertions that every patient would eventually fail therapy. Treatment Guidelines were written in accords with this belief and patients were encouraged to change treatments whenever viral loads rebounded regardless of their specific immune or clinical status.

Because in my opinion, incorrect advice was often given by these same KOLS regarding how to actually change therapies, many patients continued to burn through whatever new medications were available without achieving the goal of a sustained undetectable load.

Fortunately, many patients continued to do well in spite of drug resistance even high levels of drug resistance or multi drug resistance. However, the recommendation of the Key Opinion Leaders in HIV Medicine was often to change regimens whenever viral rebound occurred regardless of the clinical or immune status of the patient.

This in my opinion has led to unnecessary toxicity for some patients and in cases where patients were switched without really having enough active drugs to result in maximal suppression increased drug resistance to new classes of drugs potentially and unnecessarily limiting future treatment options.

How to use drug resistance to the advantage of the patient

The doctrine of achieving an undetectable viral load as the cardinal goal of therapy has led to too much clinical and research focus on strategies to get people to undetectable viral load. This has come at the expense of a lack of research on understanding the mechanisms of the viral disconnect and how to make best use of this phenomena strategically for the individual patient.

In the developing world where it is unlikely that patients with drug resistance will have access to all the new medicines discussed here, learning how to treat patients and maintain their health with some viral resistance and some ongoing viral replication is essential.

More research is needed to better define and understand the phenomena the "viral disconnect" in order to tell us which patients can safely continue their regimens in the setting of drug resistance and which patients actually need a change. An important study published in JAIDS shows that many patients with the viral disconnect are quite stable and may not need to automatically change therapies.

A study shows that many patients with drug resistance are quite stable

In this study published in Sept 2004 entitled the "Effect of Persistent Moderate Viremia on Disease Progression During HIV Therapy," patients who maintained stable viral loads but within different ranges for at least six months were compared to determine the correlation between viral load and disease progression over the next 4.3 years [2]. Patients were divided into three groups, those patients with less than 400 copies/ml, patients with between 400-20,000 copies/ml and patients with greater than 20,000 copies/ml. Patients were followed up to 4.3 years and it was found that the risk of developing and AIDS illness or dying was no different in the group with less than 400 copies/ml vs. the group with 400-20000 copies/ml. However it was much higher in the group with more than 20,000 copies/ml.

Importantly in the first year of follow up median CD4 changes were 75 cells/mm³ for the group with less than 400 copies/ml. In the group with 400-20,000 there was a positive gain but only of 13 cells/mm³ while in the greater than 20,000 group there was a loss of 23 cells/mm³. The authors conclude that "these data suggest that the maintenance of moderate viremia may confer clinical benefit not seen when viremia is greater than 20,000 copies/ml and this should be taken into account when considering the risks and benefits of continuing (virologically) failing therapy."

In fact it is surprising that there was no difference in disease progression between the group who started with a viral load of less than 400 copies/ml vs. the group who started with a viral load between 400 and 20,000 copies/ml. However that does not mean that there might not be a real benefit in maintaining a viral load of less than 400 or less than 50 copies/ml. Only longer term follow up would determine if there is such benefit.

Drug resistance strategy considerations

My conclusion from this study is that it highlights the need to take into consideration all the principles of therapy in prescribing ARV drugs and not make the achievement of an undetectable viral load the main focus of treatment.

As HIV treatment improves and less toxic meds active against drug resistant virus become available, it

may well make strategic sense to try to achieve an undetectable viral load in a patient in whom it might have previously made strategic sense to avoid changing treatment.

For every patient, it is important to balance the different considerations of drug potency, resistance, and toxicity in formulating the best regimen and deciding whether it should be continued or changed at any given point. It is comforting to gain support from this study that one should not automatically change treatment for a detectable viral load (as many experts, particularly pharma supported KOLS continue to recommend) but rather to individualize treatment in the context of weighing all the important considerations and their impact on the individual patient.

Careful monitoring of the individual patient at appropriate intervals gives the best insurance of maintaining a safe and effective regimen when it can be maintained and changing it when it needs to be changed. Achieving an undetectable viral load is what I would call a goal of therapy not a principle of therapy. It is a goal whose achievement has certain important benefits like maximizing immune recovery and avoiding drug resistance.

However, in a highly experienced patient who has already accumulated significant toxicity, an overaggressive approach to achieving an undetectable viral load could cause excess drug toxicity, further compromise future regimens or diminish quality of life. This could be a costly goal that doesn't carry with it a real health benefit. On the other hand if treatment can be improved both in terms of better viral suppression and less toxicity that would suggest a strong rationale to change and improve treatment.

Finally, the continued accumulation of clinical outcomes data as new treatment options emerge is essential to help clinicians individualize treatment and update their treatment approaches.

III. DRUG TOXICITY- My goals for my patients are long term survival, the best possible quality of life while we wait for a cure. Serious drug toxicity can undermine the achievement of all three goals. Fortunately there has been a clear cut trend towards a better understanding of toxicity and the availability of cleaner and less toxic treatment regimens particularly for newly treated patients. However, patients with significant drug resistance often have lengthy treatment histories and already may have accumulated significant amounts of drug toxicity. The amount of drug toxicity a patient has already accumulated as well as the potential for more toxicity to occur need to be strategically assessed in relation to the new regimens that are considered.

Minimizing drug toxicity requires careful monitoring of individual patients, treating metabolic complications of certain HIV meds such as high cholesterol or insulin resistance and trying to choose regimens with minimal amounts of toxicity that will allow the patient to achieve the best health outcomes. This may require strategically prioritizing minimizing drug toxicity and choosing a less potent regimen that may not maximally and durably suppress HIV.

New drugs like the integrase inhibitors or R5 inhibitors bring new hope in terms of formulating less toxic regimens as well as potent regimens that can help patients in need overcome drug resistance. But brand new drugs that may look good from a toxicity point of view in short term clinical trials done to gain FDA approval may have important toxicities that will emerge only with more extended clinical usage. Healthier patients, whether drug resistant or not may not want to rush to use brand new drugs for this among other reasons. Hopefully, it will turn out that brand new drugs can help healthier patients take less toxic regimens.

On the other hand, advanced patients suffering from AIDS complications or at risk for developing AIDS complications should not let toxicity considerations result in the exclusion of treatment approaches that can be lifesaving.

IV. COMBINATION THERAPY- The success of HAART depended upon combining drugs that when used independently have insufficient potency to suppress HIV but when used together can maximally suppress HIV. The standard for combination therapy requires that three fully active drugs be used in treatment. While it is theoretically possible that with more potent drugs just two or even one drug can be sufficient, it

has not been shown that there are any drugs of sufficient potency in highly drug resistant patients with high viral loads that adding one or even two of new and/or fully active drugs is sufficient to maximally suppress HIV.

Unfortunately for years important panels of expert clinicians like the Department of Health and Human Services (DHHS) guidelines panel have continued including as of today to recommend that new regimens contain 2 not three fully active drugs for patients requiring salvage therapy. I have always found it odd that while for easier to treat patients the DHHS Guidelines Panel has recommended three new active drugs that for the most difficult to treat patients in need of effective salvage treatment two new active drugs are recommended [3].

Historically for some patients in need of a new and better regimen three or even two new fully active approved ARV drugs were not actually available for patients in need of a new regimen. However, I feel that the continued recommendation of two new drugs has been misleading and encouraged premature and suboptimal treatment changes. In addition it led to ignoring alternative treatments that lacked a drug company sponsor. These treatments could have given the patient the third drug that was needed for success.

Sometimes drugs not specifically approved for HIV like hydroxyurea (HU) or Foscarnet might have been considered to add as an additional active agent for some patients in whom it could make the difference between success and failure of a new regimen. However, both HU, a generic and inexpensive drug and Foscarnet, a drug approved for treating CMV infection, lacked a drug company sponsor. I believe if the DHHS panel had made it clear how important it was to give three fully active drugs it would have created pressure on the NIH to devote resources to evaluating treatments like HU and Foscarnet in clinical trials.

Unfortunately, good results with hydroxyurea in clinical practice as well as in small clinical research trials have been discounted due to perceived toxicities that were caused by higher doses or combinations with other toxic agents (ie, D4T,DDI+HU,) Foscarnet's usage has been limited by the need for daily infusions and the potential complications such as serious infections that can occur in patients receiving daily infusion therapy. But until we reach a point where every drug resistant patient can be safely and effectively treated with standard therapies I believe reassessment of these approaches is in order.

What does an optimized background regimen really mean?

A new concept has emerged to substitute for that third drug which is that of the Optimized Background regimen or OBR. OBR means selecting whatever drugs might have some potency despite drug resistance or from perhaps fully active drugs that have been yet to be used by an individual patient. Medication history and resistance tests are often used to arrive at the best OBR decision.

This concept has facilitated clinical trials leading to the approval of drugs like T20 (Fuzeon) in which T 20 plus an OBR is compared to OBR alone [4]. OBR is generally left to the treating clinician to determine. An analysis of these studies, done also for Prezista and Aptivus leading to their FDA approval, indeed does show that the study drug plus OBR is better than OBR alone. Certainly when OBR plus a study drug does better than OBR alone this is an important finding which supports the FDA approval of the study drug.

However, it is failing patients in a number of important ways. Clinical trials bundle easier to treat and stable patients with harder to treat, deteriorating patients and have generous definitions of salvage as for example above 5000 viral load a level at which significant number of patients are stable and may not even require a treatment change.

For truly advanced patients three, not two, fully active meds are needed

Less reported and not properly given consideration is that these studies tend to show very low durable responses when OBR contains no clear-cut active agents. My interpretation of each of these studies is that only when 3 fully active drugs are used is an excellent response rate obtained. For example, in the initial Fuzeon studies, only 14% of patients with no active background agents achieved maximal viral

suppression at a key time point.

Even though limited information has been provided to clinicians regarding the number of active drugs in the OBR (which correlates with success) patients treated on these studies have not been sufficiently distinguished in their baseline characteristics. Patients with higher CD4 cells and lower viral loads (easier to treat) have been lumped in with harder to treat patients with high viral loads and low CD4 counts and who much more urgently need effective treatment. In addition no specific information is given about optimized background and what drugs it contains for which patients.

Thus patients and clinicians have been misled into thinking that a new drug holds more promise for salvage than it does when in fact for its promise to be fully realized it needs to be combined with other fully active drugs.

One or even two new drugs are not enough when treating the patients who need new treatment the most, patients with high viral loads, low CD4 counts and MDR-HIV. However, historically it has been the case that patients in this predicament only had one or at best two new drugs to try.

Can OBR provide the necessary potency to make a regimen work without enough active meds?

It is essential that we prioritize and strategize how to deliver three new fully active drugs to these patients. Another consideration is to think about whether within the apparent important choices of drugs that the patient is already resistant to (in the OBR) there might be specific drugs that predictably still retain some activity. It is essential that more formal clinical research be done on the potency of recycled meds in the setting of drug resistance and that the DHHS Guidelines panel incorporate this research into its recommendations.

Non standard approaches that have shown significant antiretroviral activity like boosting NRTI's with hydroxyurea or using the CMV drug Foscarnet could also be incorporated into OBR for some patients potentially increasing success rates.

But these approaches are rarely used even in situations even when they might make the difference between success and failure. In my opinion they are not used not because they are not effective but because they lack the support of pharma and our pharma sponsored clinical leadership.

Properly conducted clinical trials of these treatment approaches in salvage therapy have not been done. In addition, there has been little interest in incorporating actual clinical experience with these treatment approaches resulting in what I believe would be their increased clinical usage.

The National Institute of Health should be assuming a leadership position in studying treatments that lack drug company sponsors to meet the real clinical challenges that patients face of not enough active drugs to maximize success rates when new medications are tried on multi-drug resistant patients. Instead the leadership of the AIDS Adult Clinical Trials Group sometimes chooses to do clinical research that adds little to medical knowledge [5]. It doesn't look good that this leadership receives extensive outside consulting work from the very drug companies that they choose to allocate precious clinical trial resources to the "study" of their drugs. Transparency in clinical research is a crucial goal in a country with heavy pharmaceutical lobbying in congress and research.

Why more research is needed on optimized background regimen (OBR)

A profession more interested in patient outcomes than clinical trials that support drug companies jockeying for positioning their drugs would be keenly interested in optimizing OBR. As previously noted here, the Key Opinion Leadership in HIV Medicine including the luminaries who decide what trials the National Institute of Health sponsors have outside consulting arrangements with pharma that may bias their capability to prioritize and implement research that directly answers clinical questions regarding treatment approaches that go beyond supporting a lucrative pharma product. Obviously now that OBR has become an integral part of clinical research some research should be focused on OBR itself.

Why clinical trials can be hazardous to advanced patients seeking new option

Finally, advanced patients desperate for new options have been treated in clinical trials with OBR and the study drug or placebo potentially creating more drug resistance and blowing sometimes their last remaining effective treatment options. For example, like all other companies, the Merck integrase trial randomized its patients to receive OBR with the Merck Integrase or a placebo [6].

For example, let's say an individual MDR-HIV patient still had Fuzeon and perhaps one other active drug like Prezista available at the time of entering into the Merck integrase/placebo trial. If that patient was randomized to a placebo, it is likely that with only two active drugs (Fuzeon and Prezista) on board, resistance would develop to both Fuzeon and Prezista (POWER studies show around 30% of pts under 50 VL at week 48 for these patients).

Similarly, Tibotec Pharmaceutical randomized patients who were enrolled in its Duet study testing the combination of TMC114 (now Prezista) with TMC125 (now available in expanded access) to a placebo or TMC125. Although Tibotec had two new drugs for patients needing salvage therapy, their trial was structured to expose the patients randomized to the placebo to sequential monotherapy for six months. I believe for patients with no active drugs available in OBR that they could have made available both drugs simultaneously.

It is of little help to the patient that after 16 weeks as specified in the Merck integrase/placebo trial they could then get the Merck drug because of virological failure as the trial allows. In fact now with only the Merck drug as active the patient is likely to develop resistance to that too and as a consequence of participating in the trial could have new, unnecessary and compromising drug resistance to Prezista, Fuzeon and the Merck integrase inhibitor. Had these three new meds perhaps been taken together, it would have been that patient's best and perhaps only remaining shot at effective combination therapy.

Similarly the Duet study recently conducted by Tibotec randomized some advanced multi-drug resistant patients to a new non-nucleoside drug called TMC 125 or a placebo along with the new protease inhibitor Prezista (then called TMC114). Without any protest from the Key Opinion Leadership in HIV medicine this trial exposed some advanced patients to TMC 125 in clearly suboptimal combination therapy regimens potentially resulting in resistance to this agent. There may be patients for whom this drug would have been a key component in a lifesaving combination therapy regimen when given in a properly formulated regimen.

Patients and clinicians should weigh carefully the consequences of participating in trials that expose the patient to sequential therapy (known to be substandard). Pharma and the Pharma sponsored KOL Leadership should do more to design trials in a way to minimize this risk and avoid it completely in advanced patients whose lives may depend upon them receiving combination not sequential therapy.

In the Merck trial patients were eligible for viral loads of greater than 5000/copies per/ml. This lumps healthier, potentially easier to treat patients who have lower viral loads with highly advanced drug resistance patients with very high viral loads. For these advanced patients participation in the Merck trial may have represented their last remaining chance for effective therapy. Some of the most advanced patients might not in the opinion of their doctors been able to survive long enough without better treatment to wait until the Merck drug was more generally available. I believe those patients should have all been given the Merck drug and not the placebo.

For healthier patients the consequences of getting a placebo and even potentially developing new drug resistance may not have any lasting adverse clinical impact. But for the advanced patient the difference between getting a placebo or the drug may be life or death. Expanded access or open label access for patients in need should be started as soon as phase II safety and dosing data are obtained

I feel very strongly that this situation isn't right either scientifically or ethically. I believe very advanced patients with MDR-HIV, very low CD4 cells and high viral loads especially when clinically ill should not be

given placebos nor should the data gained from their participation be mixed in with healthier patients potentially confusing the results.

Open label compassionate programs that provide access to multiple investigational agents, when possible, should be facilitated for physicians treating these patients. The activist community should make this a high priority, no matter how small the number of deep salvage patients may be in the future.

Recently progress has been made in identifying and addressing this priority in the activist and medical community. AIDS Treatment Action Committee has issued recommendations regarding the conduct of clinical trials in HIV medicine to better meet patients' needs. Please refer to the "Statements of beliefs & demands document" linked here: <http://atac-usa.org/ddc/ddchome.htm>

What is really needed to improve salvage therapy and help the "invisibles"

With so many new drugs available for HIV and the complicated and even confusing treatment situation presented by very advanced patients we in HIV Clinical Medicine desperately need a treatment registry in which the data from all of these patients could be entered into and analyzed for patterns of response including antiviral and immune response, toxicity and survival data.

There needs to be an agreed upon definition of patients who urgently need new treatments and might be compromised irreversibly by getting a placebo. The drug companies, the FDA, and clinicians could learn about the way these drugs work in this population by entering these patients into a treatment registry and carefully following these patients over time.

The technology exists to inexpensively and efficiently enter these patients clinical and lab data into a central treatment registry. Similarly this data could be reported and analyzed at regular intervals. Big Clinical labs make huge profits on the blood testing of the HIV infected patients but as far as I am aware do little to contribute to clinical research in HIV Medicine. They could be called on to contribute to this effort.

I call on my colleagues particularly at the AACTG to shift the focus and resources from conducting studies on already well studied and long in clinical usage co formulated drugs like Truvada and Epzicom that benefit pharma more than patients. Instead, their attention should be shifted to the plight of advanced patients. Resources need to be committed to learning how to treat these pts most effectively with new and older meds.

V. DRUG INTERACTIONS AND DRUG DOSING- are key technical considerations in formulating new treatment regimens.

A regimen can be defeated if one drug (not necessarily an HIV drug) interferes with the metabolism of an HIV drug. There was uncertainty regarding the usage together of two of the newest drugs the Merck Integrase inhibitor and a new NNRTI called TMC 125 which have just become available in expanded access. Both companies had sufficient concern regarding the potential for an unfavorable interaction that each company initially was forbidding the usage of its drug with the other. Studies that define this drug interaction fortunately have just been completed and it appears that the drugs can be safely used together.

It may be prudent for highly resistant patients that need 3 fully active drugs in a new salvage regimen to achieve the best clinical outcome to sometimes wait until drug interaction issues are clarified. Again treatment decisions have to be individualized because some ill patients may not be able to wait until drug interaction data is fully available. Patients were not allowed to apply for TMC 125 with Pfizer's R5 entry inhibitor Maraviroc until August 2007 because of concerns about an unfavorable drug interaction.

Situations in which there are potentially hazardous unknowns regarding the usage of new drugs raises the question of whether there are stopgap measures that can be used to stabilize a patient long enough to wait for new therapies or new information about those therapies. I will address this later.

VI. DRUG ADHERENCE- Great progress has been made in treating patients who have no drug resistance with much easier to take and safer regimens such as Atripla a one pill a day combination of Sustiva, Viread and emtricitabine. When patients are asked to take cumbersome and difficult to tolerate regimens such as those sometimes needed in deep salvage treatment a great doctor patient relationship is essential that includes a clear description of what the regimen is going to take on the part of the patient and a commitment to manage side effects and toxicities attentively and supportively.

I believe here it is very important to emphasize the ultimate goals for treatment, long- term survival, avoiding sickness and improving quality of life. Sometimes it takes time for a patient to come around to the prospect of taking a difficult to take treatment like Fuzeon and treatment needs to be individualized. In the case of Fuzeon I believe it should be emphasized that as new drugs become available it may be possible to substitute for Fuzeon a less cumbersome drug.

Since Fuzeon is a very safe and effective HIV drug indispensable at present to formulating successful regimens for some patients I believe we need to do more to encourage its proper usage. Patients need to clearly understand the risks of suboptimal and sequential treatment and much more support and recognition needs to be given to the challenges patients face in taking this medication.

VII. DRUG COST AND ACCESS- Although great progress has been made in making available standard HIV therapies to HIV infected individuals in all strata of society progress needs to continue. In my opinion a pharma sponsored Key Opinion Leadership has wasted time and precious clinical resources on helping drug companies market "me too" (explain) drugs instead of focusing on key clinical questions regarding therapeutic strategies. In addition, some of the most talented and knowledgeable clinicians have opted out of clinical practice in favor of pharma sponsored medical education which diminishes their awareness of the intricacies of the current treatment landscape that they are educating their colleagues about as well as directing new research.

Resources for HIV treatment and research while relatively abundant in the developed world are not infinite. The US annual cost of Fuzeon + Prezista+ Norvir + Truvada is close to \$40,000! Recently some patients have possibly died while on waiting lists for resource restricted ADAPS [7]. There are opportunity costs in money wasted that could be used more effectively in both medical research and practice.

For example, the same ADAPS that maintain waiting lists pay routinely pay for boosted Lexiva at a big extra cost even though it is no better than the standard of care Kaletra for most patients. It seems to me it would make sense to not have boosted Lexiva on resource restricted ADAPS formularies. The potential cost savings could allow for patients on the waiting list to get benefits.

Integrating Principles of Therapy into Actual Clinical Practices

In summary, I believe a careful consideration of the above principles of therapy tailored to each patient's treatment needs and goals are essential to optimize therapy in an evolving treatment landscape. The benefits and drawbacks of a proposed regimen need to be weighed in terms of each of these considerations or principles. To complicate matters further as we evolve our understanding of how HIV damages the immune system and causes illness in infected patients it is clear that a more sophisticated principles of therapy should include a consideration of some new principles of therapy.

A more sophisticated and useful understanding of how HIV damages the immune system

One of the hallmarks of untreated HIV is its tremendous variability from patient to patient in damaging the immune system. It takes on an average of 11 yrs in an untreated patient to get sick with some patients getting sick more quickly and some patients maintaining good health without treatment for over two decades.

Much research over the years suggests that much of this variability is a function of how HIV and the immune system interact in individual patients. It seems that an over-activation of the immune system, induced by HIV, drives much of the CD4 loss that eventually causes disease. Research on this phenomenon is incomplete and ongoing. A prominent clinical researcher, Dr. Michael Lederman has reported that most of the CD4 loss in chronic HIV infection is caused by immune activation and not the amount of viral replication [8]. In addition, Dr. Steven Deeks has characterized an "Immune Set Point" achieved early in HIV infection that predicts subsequent CD4 loss powerfully and independently of viral set point [9].

In the same way that using markers that predict disease progression is invaluable in deciding even today when treatment should be initiated, these markers could and should be used in patients on treatment with drug resistance in terms of deciding who needs to change treatment and how. For example it has been shown that patients who develop viral rebound and drug resistance who maintain lower immune activation tend to have stable or rising CD4 counts vs. patients whose immune activations are higher. Patient with more activated immune systems are more likely to suffer T cell declines. Immune activation measurements could be used to identify patients who have a more pressing need for a treatment change.

As we learn more about drug resistance we are learning that for some patient's drug resistance appears to impair the virus's ability to contribute to CD4 cell loss. Patients with lowered viral fitness may also have less urgent need for treatment change and in fact a less fit virus might require less treatment. In fact if a patient with small amounts of viral replication has a virus that is evolving to a less fit virus then there may be indeed benefit in letting that evolution continue even if it involves the acquisition of new mutations.

A very important study shows some patients maintain very low viral loads despite resistance - Why?

Amazingly, a new study suggests that the hallmark of a group of patients maintaining low viral loads despite MDR HIV is the appearance of "minor mutations" that are not thought specifically to cause viral resistance to particular drugs but appear spontaneously over time in patients with ongoing viral replication [10].

It seems reasonable to consider that patients with very low viral loads should be tested to see if they have these minor mutations both for clinical practice and research needs. Many important clinical research questions need to be answered to better understand this phenomenon. Do certain treatment pathways correlate with the development of these mutations?

Can the development of these minor mutations even be facilitated by certain treatments or patterns of treatment response? Do pathways to effective treatment exist which do not depend upon the achievement of a sustained undetectable viral load such as when patients who develop minor mutations maintain very low and stable viral loads despite significant drug resistance and ongoing low level viral replication.

Drug resistant patients can sometimes actually evolve to less, not more, meds

In my own practice, I have found (which I will discuss later) that some patients, even those with a history of immune and viral failure, have been able to evolve to minimalist regimens with drugs that they seem to be completely resistant to. I have not tested these patients to see if some of them have large numbers of minor mutations but would like to do so. Patients who have sustained low viral loads and stable or improving CD4 counts despite drug resistance can potentially have the more toxic components of their ARV regimens stopped or substituted for less toxic meds.

Is there an alternative pathway to successful treatment other than maximal viral suppression?

There may be another pathway to successful therapy for some patients that depends not on the achievement of an undetectable viral load but rather by achieving and perhaps sustaining for a period of time low levels of viral replication. In fact, I will state my own clinical experience as a hypothesis that

should be a focal point of research. Are there treatment pathways that enable patients to evolve to less medication and less toxic medication even sometimes in the face of ongoing viral replication?

How a treatment registry could provide information on this treatment pathway

Because quite a number of patients are doing extremely well even after and perhaps because of the development of certain resistance mutations it seems that it would be a potentially very fruitful area of research to study whether certain treatment pathways and/or certain specific mutations or patterns of mutations are associated with a durable viral disconnect response? Some research has been done on this question, but very little in proportion to its potential significance.

There is a huge potential database that exists but may not be available to identify such patterns of mutations and treatment pathways. Just a few commercial laboratories do most of the resistance testing for HIV patients. Recently, I asked one of the clinical directors of an important and pioneering company that does resistance testing whether or not the data bank of his company could be used to study such questions. He told me that new Federal government regulations supposedly in part implemented to protect patients' privacy called HIPPA regulations would likely prohibit the usage of such information in that way. Could an informed consent form when a patient gets blood drawn that most patients I believe would gladly sign get around this use of data?

A way of protecting patients' privacy at the same time their real interests like progress in research are also protected needs to be found. Here, we need the leadership of our publicly supported NIH but the leadership at the NIH needs to recognize the kinds of questions that deserve their focus. Perhaps if NIH panel members form outside consulting arrangements with commercial labs similar to their arrangements with drug companies we may see more of this kind of research.

Added into the mix of new considerations may be a consideration of HIV specific immunity and the possibility that over time patients with low viral loads may develop HIV specific immunity that may help a suboptimal antiviral regimen from the point of view of combined potency lead to a highly effective durable regimen.

A recent paper in the journal AIDS concluded that "Persistently low viral replication (<10,000 copies/ml during antiretroviral therapy stimulates high frequencies of HIV specific CD4 and CD8 T cells compared to full virus suppression or complete virus failure. The association of high anti-HIV activity with large numbers of HIV specific CD8 cells contributes to the control of viral replication. Ref AIDS author Alatrachi jan 2005 p25-33

Thus over time as HIV specific immunity emerges in these patients these patients may be easier to treat and stay stable even when drug resistance diminishes the potency of their antiviral meds.

Thus to the initial seven principles of therapy I might add:

8. IMMUNE ACTIVATION/IMMUNE PATHOGENESIS
9. VIRAL FITNESS
10. HIV SPECIFIC IMMUNITY

I believe that a more sophisticated and useful model of therapy to apply to the treatment of patients with drug resistance should include consideration of these principles.

How to actually treat the advanced drug resistant patient with principles of treatment

Now I would like to turn the attention back to the most pressing concern in HIV Clinical Medicine How to treat a highly drug resistant patient with a high viral load and low CD4 count at risk or already struggling with AIDS complications.? Let's approach it by applying the principles of therapy we have just elaborated here.

My first concern is how to come up with a combination therapy regimen sufficiently potent to have a reasonable chance of maximally suppressing HIV replication. If I feel unsure about the ability of my best regimen to achieve that goal then I have to carefully consider if it might make sense to wait until I have more confidence. I might want to wait for a new and currently unavailable drug is made available or in the case of TMC 125 and MK confirmatory data that showed both can be used together. But sometimes you cannot wait if a patient is declining clinically.

I need to emphasize here that the decision to change treatment or not is a very individual one that needs to be done as part of the doctor patient relationship. It may be appropriate, necessary and potentially lifesaving for a treatment change to be made even when the chance of complete success is small.

Nothing in this essay should be construed as medical advice about what to do in specific clinical situations even one that may resemble one of those discussed here. Rather questions and concerns that might be stimulated by this treatment manual should be brought to the treating doctor for consideration in the context of the doctor patient relationship. (this should be in the front of the manual!)

How to individualize salvage therapy based on doing simple math

Earlier I mentioned that the viral load of the patient gives me some info regarding how potent a regimen needs to be. If a patients' viral load is 100,000 copies/ml then in order to get that patient's viral load close to undetectable I need to come up with a regimen that can drop the viral load by 3 factors of 10 or 3 logs (100,000 to 10,000, to 1000 to 100). In my math I give a fully active drug a score of 1 log reflecting its ability to drop the viral load by a factor of 10. Most fully active drugs can decrease a patient's viral load by one log or a factor of ten.

I then look at the resistance testing and the treatment history of the patient. I then try to determine if there are enough potent drugs using both newly available and older meds to achieve the log drop in viral load necessary to help the patient reach an undetectable viral load. I need to know that my newly constructed regimen will have at least 3 full logs full of potency that ideally requires three different fully active drugs. I try if possible to overshoot this goal rather than risk undershooting it. Under treatment will probably have the consequence of treatment failure, new drug resistance and further diminishment of treatment options.

Expert clinical guidance is required to make sure that drug interactions that can occur with the introduction of new meds through proper adjustments in the doses of the relevant medications.

A few examples of how to use salvage therapy math

For the purposes of illustration I will highlight examples in patients with extensive drug resistance to all three major drug categories including some patients who may have already tried some of the newer drugs. Some highly treatment experienced patients may or may not have drug resistance to one or both of the recently approved protease inhibitors Prezista and Aptivus even prior to using these drugs.

Resistance testing can help determine whether or not these drugs are active. Let's say in a particular MDR-HIV patient with a viral load of 100,000 copies/ml the new protease inhibitor Prezista is indeed fully active. Then I need two drugs. Now that I can get raltegravir (Mercks integrase) on expanded access I need only one additional drug.

If the patient has never taken Fuzeon I can feel pretty confident I've got what I need in terms of potency with three fully active drugs, Prezista, raltegravir and Fuzeon provided the patient is willing to take Fuzeon. If the patient is reluctant to take Fuzeon I will do my best to persuade the patient to try it.

But what if the patient has just failed a regimen containing Fuzeon or is unwilling to take it and I am still one short? Perhaps now that TMC 125 and Merck integrase seem not to unfavorably interact I can enroll the patient in expanded access for TMC 125 as well giving me three fully active drugs to treat my patient.

However, let's say the resistance testing in a particular patient shows that due to high levels of protease resistance neither Aptivus nor Prezista are likely to be active in addition to Fuzeon not being an option.

Unfortunately not every MDR-HIV patient's virus is sensitive to both or even one of the new protease inhibitors Aptivus and Prezista. Resistance testing and correlation with clinical experience is still needed to better define the utility of these drugs. If a genotype and phenotype show resistance to these drugs I would not count on them as fully active and adjust one's expectations and the regimen accordingly.

Thus, in this example, I can still offer the patient only two new drugs when I believe the patient really needs three fully active drugs. These are the options as I see them in this situation.

1. Give TMC 125 and MK with OBR but unless OBR can equal the potency of one drug it will fail unless MK and or TMC 125 are indeed super potent and each produce much more than one log drops. Although the Merck integrase inhibitor does appear to be more potent and may contribute more than a one log viral load drop, TMC 125 based on clinical trials seems at best to provide a one log viral load drop.

2. If I am skeptical of my ability to get the equivalent of a full drug out of OBR then I would carefully consider holding off on MK and TMC 125 at least for a short while depends on the urgency of a treatment change.

3. Another potentially challenging situation may occur if the patient has a high level of NNRTI resistance which may nullify the efficacy of TMC125. Thus even if my patients virus is sensitive to Prezista or Aptivus but has high level NNRTI resistance I still may need a third active drug or its equivalent from OBR to successfully treat the patient. What to do?

Hopefully, but to complicate matters further Pfizer's CCR5 receptor inhibitor Maraviroc is now available in expanded access and has been recently FDA approved in August 2007. This may give some patients that third drug needed to give patients the best chance at sustained maximal viral suppression. This potent and apparently well-tolerated drug (at least in the short term) has one major shortcoming in that it is only effective in patients who have an R5 tropic virus. Since only about 50% of advanced patients have a virus that exclusively binds to the R5 receptor on the surface of their CD4 cells, it is only effective in fifty percent of these patients.

However, it is extremely encouraging that yet another new drug with a different mechanism of action will soon be available. As soon as the tropism assay is available to screen patients for eligibility for Maraviroc it should be performed to evaluate advanced MDR-HIV patients for this option.

Drug interaction studies have recently been completed for Maraviroc and TMC-125 and usage of these two drugs together is now permitted if dose adjustments are made in the Maraviroc dose.

The key point is that whether using older, newer or experimental drugs the basic principle of needing three active drugs in combination is essential to treat an MDR-HIV patient with a higher viral load needing salvage therapy.

My interpretation of all the data from the TORO studies on Fuzeon, the RESIST studies with Aptivus and the POWER studies with Prezista support the validity of this simple mathematical model. Patients not starting enough active drugs in fact at least three fully active drugs or two fully active drugs and OBR equal to one fully active drug are likely to fail.

It's too bad that this point hasn't been recognized or stressed properly by the KOL'S educating the profession and patient community about salvage therapy. Previously done clinical trials of new drugs led by the same KOLS exposed patients to suboptimal salvage therapy with two and sometimes only one active drug. Although historically in some clinical situations there were not enough active drugs to give a salvage patient this should not have led these KOLS to incorrectly conclude and advise that two not three new active drugs were necessary for salvage patients. Sentence needs to be split in two!

In addition, approaches that might have given patients that third additional active drug like HU boosted NRTI's or Foscarnet were ignored or dismissed as ineffective by these experts. Of note both these approaches lack a drug company sponsor.

Do study results released on the Merck Integrase exactly support the need for three, not two, fully active drugs?

Just as I was finishing the last edit of this manual Merck reported the results of its integrase inhibitor studies at the February 2007 CROI meeting. A combination of the new main studies called BENCHMRK (NO A) 1 and 2 were presented. Both studies compared the Merck integrase inhibitor given with OBR versus OBR alone without the Merck integrase inhibitor.

From treatment activist Tim Horns article in POZ Magazine,

"Treatment results were best in those who started therapy with Fuzeon and/or Prezista. Among those who used both Fuzeon and Prezista a whopping 98% of patients had viral loads below 400 at 16 weeks compared to 87% who combined both drugs with a placebo. Among those who used Fuzeon without Prezista 90% in the Merck integrase group vs. 63% in the placebo group had viral loads drop below 400 at 16 weeks. Similar results were seen in those who used Prezista without Fuzeon [11]."

Of note although this study was conducted on patients with a significant amount of drug resistance the median T helper cell count at entry was about 150 suggesting that many of these patients might have been stable and as I will discuss in detail later easier to treat. Also 16 week results may not translate into durable suppression for some patients. Clearly though two active drugs gives better results than one new active drug and three drugs give better results than 2 active drugs.

For more difficult to treat patients with higher viral loads and/or less active agents in their OBR I would expect the differences between using 2 vs. 3 active drugs would be more dramatic in favor of 3 new drugs.

In fact data presented stratifying patients into those who started the trial with above vs. below 100,000copies/ml were presented. Among those who entered the study and received the Merck integrase inhibitor with greater than 100,000 copies/ml 64% achieved the less than 400 copies/ml benchmark at 16 weeks vs. 88% who achieved the benchmark who entered the study with less than 100,000 copies/ml.

Unfortunately a subset analysis breaking down the groups of those starting the Merck integrase inhibitor with above or less than 100,00 copies/ml into those receiving either one or two new agents (Fuzeon and/or Prezista) was not presented. I'm sure it would have shown more dramatic differences in success rates for patients in the higher viral load group who got 3 not 2 new active drugs.

Could a treatment registry for salvage patients improve treatment for all such patients?

Sometimes in patients treated in clinical practice it is not that clear even after a careful assessment of the patients treatment history, resistance profile and available medications whether a salvage regimen will work for an individual patient. Sometimes the actual activity of drugs newer, older, or recycled is not clear enough to be confident about the potency of a proposed combination regimen. But yet there is pressing clinical need to improve treatment and clinicians want to give their patients the best possible regimen.

A treatment registry tracking actual outcomes of advanced patients on salvage would be invaluable. By tracking the patterns of response and clinical outcomes we could better discern which combinations work or don't work in which kinds of patients. This could help clinicians make better recommendations for these challenging patients.

Such a registry would not highlight a particular drug company's drug but rather a type of patient in need of better therapy, the advanced patient with MDR-HIV. The focus of the registry would not be on the individual drugs but rather how the drugs are used in combination and the outcomes of those

combinations. This registry would reflect the prescribing of drugs used in accordance with our best understanding of principles of therapy including how those principles are applied by individual clinicians.

This registry, of course track the outcomes of all patients in salvage situations including those patients in who physician and patient elect to hold off on new medications strategically or sometimes based on patients preferences. Who knows what unexpected but important information about drug interactions or toxicity would be uncovered in this registry with all these new drugs used in new combinations.

It comes as no surprise to doctors that our patients sometimes prefer not or cannot follow what we regard as our best recommendations for any number of reasons. I believe that a treatment registry that tracked and reported on outcomes could be useful to doctors trying to persuade reluctant patients to try new therapies if evidence was presented from such a registry.

I also believe that patients and doctors would reawaken to the fact that the care of the individual patients has ramifications for the community of patients and such a registry would encourage doctors and patients alike and demonstrate our scholarly commitment to our patients beyond that supported by drug companies.

For advanced patients, anti viral therapy is just one component of the patient's medical treatment. Advanced patients can still present a host of medical problems that require diagnosis and treatment such as infections and malignancies. Opportunistic Infection (OI) prophylaxis including for PCP, CMV and MAI is often necessary to lessen the likelihood of some very immune compromised patients getting sick. Medical problems and the treatments they require can interact with or even interfere with HIV medication. Given the complexities, again a treatment registry would be very valuable to clinicians trying to balance sometimes even conflicting therapies and problems.

Treatment interruption is usually a bad idea- an example of research into treatment strategy

Studies of advanced patients focused on treatment strategies rather than individual medications have already yielded important results of the kind I believe a treatment registry would uncover. For example, the evidence is pretty strong that stopping ARVS altogether in a failing regimen is too hazardous as a treatment strategy [12]. It was hoped that by stopping meds altogether patient's viruses might be re-sensitized to drugs to which they were resistant allowing for these drugs to be recycled in the next regimen and contribute new activity. However, it appears that even when there is extensive drug resistance some meds have residual potency that is lost if all the meds are stopped. Most importantly, these studies show those patients off meds are much more likely to get sick.

Recycling and adjusting meds

There is evidence that most of the activity in a failing regimen is in the NRTI's, not the protease inhibitors but no good study in my opinion shows that withdrawing proteases in these patients is the right thing to do. There is evidence that stopping the NNRTI (Sustiva, Viramune, or Rescriptor) as soon as resistance develops is a good idea. Once resistance develops these drugs have little to no activity. Continuing an NNRTI can cause higher levels of NNRTI resistance potentially leading to cross-resistance to TMC 125 thus taking away this potentially important option.

One med I might withdraw is Fuzeon in the hope of recycling it in a new regimen. Measurable Fuzeon resistance tends to disappear in some patients (not in all of us) in 12-16 weeks off the drug which may enable it to be recycled. Even when Fuzeon resistance is no longer measured by resistance testing it is likely that there are still Fuzeon resistance strains that are present in the patient at low levels but not picked up by resistance testing. If Fuzeon was restarted without anything else changed these "archived" Fuzeon resistant virus would quickly emerge and neutralize any antiviral activity of Fuzeon.

I believe that when Fuzeon is restarted however with multiple new active drugs it may still contribute important antiviral potency in this setting. Here's why? Let's say there are only two out of the three new drugs needed for maximal suppression present when a new treatment including recycled Fuzeon is

started. In this situation for the virus to breakthrough the archived Fuzeon virus needs to acquire mutations to the two new active drugs to breakthrough as a new MDR-HIV. However right from the start Fuzeon is working with the other two new drugs to rapidly reduce viral load which reduces quickly the pool of viruses that resistance can emerge from and the two new drugs are still active against the Fuzeon resistant strain until it acquires mutations to both drugs.

Sometimes recycled drugs can contribute important potency to salvage regimens. A Treatment registry would help identify which drugs in which clinical situations could be effectively recycled.

However in certain patients who are already ill it may be too risky to wait on improving their treatment. Some advanced patients clearly need the best ARV treatment we can come up with at any given time. Although these patients fortunately are a small percentage of patients needing better salvage therapy their treatment is critical and challenging. I would want to see if there are any other ways I could get some more "juice" or potency in their salvage regimens and increase the likelihood that the use of raltegravir will result in a sustained response to a transient response followed by resistance to raltegravir.

Two little used treatments with significant potential: Foscarnet & Hydroxyurea

Two approaches should be considered here both with advantages and significant drawbacks.

1. Foscarnet, an FDA approved drug for CMV disease, is a very active anti-HIV drug and in my opinion is a fully active drug based upon small clinical trials and my own clinical experience. It has the drawback of requiring a lengthy and cumbersome infusion 2x a day at least initially and has potential risks for serious toxicities like kidney damage, anemia, and even seizures and infections related to the indwelling catheters needed for its daily administration [13]. However, if the patient is properly motivated and monitored it can be lifesaving.

In addition, many of the patients with the kind of advanced disease meriting consideration of this treatment also have active CMV disease that the Foscarnet can effectively treat. In my practice I probably have used Foscarnet for varying periods of time of several weeks to several months in two to three patients a year. In my experience it has been incredibly effective and lifesaving and some of the patients whose lives I believe it has contributed to saving have been able to move along to better and more durable therapies as new drugs have come along.

An oral form of Foscarnet, actually an NNRTI, is slowly moving its way through clinical trials and hopefully will become available to patients in the next several years.

2. Hydroxyurea (HU). The other potential place to find the equivalent of a fully active drug in the setting of extensive drug resistance is by considering the recycled use of Zerit (D4T) and (3TC) Eпивir either alone or with hydroxyurea.

An Old Study Shows D4T/3TC and HU is Unexpectedly Quite Potent

It's been ten years since Steven Miles and Peter Ruane reported heavily pretreated and protease and NRTI resistant patients with fewer than 50 T cells and an average viral load of 100,000 copies had a response to a salvage regimen of D4T, 3TC and hydroxyurea with an average 2 log drop in viral load [14]. They also reported neutropenia and a lack of a CD4 cell improvement that suggested this approach needed further clinical study [15].

In my own practice, I have found that D4T/3TC and HU have added enough additional potency to the OBR to help some patients with only one or two new active drugs to achieve and sustain maximal viral suppression. As I have gained experience with this approach I have often found that lower dosages of D4T and HU than used by Dr. Miles has been effective which I believe reduces then toxicity of this treatment approach.

Clinical studies are needed to further validate this approach

Unfortunately despite these impressive results to my knowledge a proper study randomizing patients in salvage to OBR with and without D4T/3TC/HU has not been done. A comparison of D4T/3TC with or without HU would also be important to do since D4T/3TC often has significant potency even in the setting of high levels of NRTI resistance.

In my opinion the consequences for HIV infected patients in not having these results properly followed up on and tested in clinical trials has been enormous if those trials were to show as I believe they would strong antiviral potency of D4T/3TC/HU in salvage.

Recycled D4T - another explanation for success of hydroxyurea?

One of the important alternative explanations for the success if HU in some of my patients is that I started it with recycled D4T in many patients. Recycled D4T itself or recycled D4T and 3TC might account for the success of some of the patients reported by Miles and Ruane and in my practice. There is a growing body of evidence suggesting that D4T has significant potency in the setting of resistance even with significant NRTI resistance.

Should recycled D4T be considered for inclusion in OBR despite toxicity concerns regarding its usage?

D4T's potency in the setting of MDR-HIV including multiple nucleoside mutations should strongly commend it for consideration in the treatment of the MDR HIV patient in whom every bit of potency available needs to be called on to give a difficult to treat patient a chance at achieving and sustaining an undetectable viral load.

Despite D4T's unfortunate toxicity and contribution to lipodystrophy, much of which may dose related, I believe that in accordance with a careful weighting of the principles of therapy, D4T may be underused in patients who may need it. Starting tenofovir for example instead of D4T is clearly the right move in newly treated patients. It is also a good move to substitute tenofovir for D4T in appropriate patients doing well on treatment to reduce toxicity. However, using tenofovir and 3TC in advanced MDR-HIV as OBR as I suspect is often done I believe provides little to no potency as compared to D4T. I'm not aware of any data showing unexpected potency of tenofovir in MDR-HIV such as exists for D4T.

A recent study [16] showed that the addition of D4T to a virologically failing regimen, in patients with significant genotypic resistance to D4T had impressive viral load drops measured 1 month after adding D4T. Forty patients were studied and after 4 weeks the median viral load drop was 1.28 logs. reference

Interestingly, the study's investigators looked at the specific mutations patients had prior to adding D4T. They found that certain mutation patterns were associated with varying degrees of response to D4T ranging from a minimal response of a .26 log reduction in viral load to an impressive 2.15 log drop in viral load.

The study included patients with a wide range of viral loads; Median 13,950 cps/ml range 1,830-346,000 and a wide range of CD4 cells mean 314mm³ and range (100-642).

Thus these were not truly advanced patients. Also the durability of the viral load drops were not assessed because after 4 weeks on D4T other treatment changes were made and no follow-up after 4 weeks was reported. I believe that most highly drug resistant and advanced patients are usually given Viread instead of D4T. This may be a mistake in patients needing every bit of potency in OBR. Again a treatment registry might shed light on this issue that is unlikely to be subjected to a clinical trial.

It would be of great interest to see whether lower doses of D4T, potentially associated with less toxicity

might produce similar viral load drops with or without HU. There is one important caveat in interpreting the significance of these results in terms of patients with advanced MDR-HIV and high viral loads.

D4T - Dosing and Toxicity - Lower doses of D4T may reduce wasting and toxicity

Some recent clinical research has been done to investigate lowering the D4T dose from 40 mg 2x a day to 30 mg 2x day would affect measures of D4T toxicity such as fat loss, increased triglycerides, and increased cholesterol. 58 patients in a Spanish study who were already undetectable, and already on combination therapy regimens containing 40 mg 2x day were randomized to continuing Zeret 40 mg 2x day or switching either to Viread 300 mg 1x a day or Zeret 30 mg 2x day [17]. All patients changed to 30 mg 2x day maintained undetectability and both the Zeret 30 mg 2x/day and Viread groups had increases in body fat while the D4T 40 mg 2x day continued to lose fat. However, the results were not reported to reach statistical significance meaning that chance could not be conclusively excluded as accounting for the results.

Is the treatment of healthier MDR-HIV patients different than the treatment of more advanced patients?

The last topic I want to address here in more detail is the treatment of healthier, less immune suppressed patients who have some degree of viral replication and drug resistance. These patients have been categorized as previously discussed as having a viral disconnect between their viral load and CD4 cell counts. This term is slightly misleading since most of these patients have significantly lower viral loads than their baseline viral loads prior to treatment. This lower viral load allows for improved or stable CD4 counts in these patients.

As earlier discussed the mechanism accounting for the viral disconnect in which viral load rebound and resistance to antiviral medication is probably a combination of the reduced fitness of the resistant virus as well as residual potency of some of the antiviral meds even when resistance is measured such as with D4T. In addition, over time evolving HIV specific immunity and/or the development of minor mutations may contribute to the maintenance of the viral disconnect in some patients.

Although the focus has been to try to re-suppress patients to an undetectable viral load with new medication regimens, I believe the proper strategic approach is to carefully apply principles of therapy on an individual patient basis and in particular give important weighting to toxicity concerns. Here's why?

One of the justifications usually given supporting changing regimens to try for maximal suppression is that many KOLS worry that once resistance develops to a medication within a particular class of medications such as nucleosides or proteases that over time higher levels of resistance to that medication will occur. In addition cross-resistance to other medications within that class will develop. As time passes for patients who continue to take a failing regimen gradually higher levels of resistance could develop that could severely limit future treatment options in that class of medications.

Although it is usually not stated this way, another concern is that higher levels of resistance will further reduce whatever residual activity a drug has in the setting of drug resistance.

As earlier discussed, for very advanced, sequentially treatment patients, indeed this very scenario played out catastrophically for some patients who received the first protease inhibitors and who had little subsequent treatment options after resistance including cross-resistance developed to protease inhibitors. However, fortunately for healthier patients and sometimes for more advanced patients another scenario plays out as described by the viral disconnect.

Clearly, if viral disconnect patients never change therapy; some patients will progress to advanced disease. Indeed one study suggests that after several years some patients return to baseline CD4 counts [18]. The previously discussed Rafferty study suggest, however that patients with less than 20,000 viral loads are not at particular risk for disease progression in 5 years and may be candidates to continue their

treatment unchanged with appropriate monitoring.

Are some viral disconnect patients with drug resistance getting easier to treat?

Based on my clinical experience and my interpretation of a number of recent studies in this light, I believe something else is going on as time passes for many patients on treatment that have developed some degree of drug resistance. I believe with the passing of time there is a category of patients who have ongoing viral replication and drug resistance who become easier and easier to treat. For these patients, less potent regimens are quite effective and, as in the case of some of my long term treated patients who have had HU in the mix of their medications, some patients can be even maximally suppressed with drugs that they are genotypically and phenotypically completely resistant to.

Is there an "alternative treatment pathway" that does not depend on maximal viral suppression?

As patients get easier to treat, despite drug resistance and likely in part because of drug resistance then these patients have expanded list of treatment options including drugs to which they measure as resistant to. As their options increase and also because maximal suppression is not as high of a priority the focus can shift to what currently concerns many patients and clinicians the most, which is drug toxicity.

These patients can have treatment changes driven by the focus to lessen the toxicity of the regimen more than to maintain an undetectable viral load.

I believe that the number of patients who can succeed on this alternative treatment pathway is quite more than even doctors who have given this some consideration, including myself, is higher than we might imagine.

The ultimate measure of success of this treatment pathway is whether patients achieve our goals of long term survival and excellent quality of life again. Only by following patients over time in a treatment registry analogous to the MACS study will we learn whether for some patients outcomes are even superior on this pathway.

Of course more research is needed to fully support this approach which up until now has been driven largely by necessity in that the lack of enough new drugs to maximally suppress HIV or toxicity concerns kept patients from automatically changing treatment and in my practice sometimes adding HU into the mix of meds.

It may be that with new, more potent and safer meds that maximal suppression will be the way to go anyway for most patients but with new drugs experience has taught us that there is unfortunately quite a lag between studies demonstrating efficacy and clinical experience showing toxicity.

However, the general notion that some patients are getting easier to treat has relevance for both fully suppressive and partially suppressive treatment strategies. Several recent studies I believe support this interpretation of an easier to treat patient responding better to less treatment in the setting of drug resistance.

Do recently published clinical trials support the notion that over time some patients are getting easier to treat?

A just published French study ANRS CO8 [19] reported very good results in using Kaletra in a heavily pretreated population with extensive drug resistance. Included in this group of 121 patients were 40 patients treated just with Kaletra. Ninety-five per cent of patients had genotypic mutations associated with Kaletra at the time of Kaletra initiation.

Despite this resistance to Kaletra the authors concluded "the use of Kaletra in HIV infected patients failing multiple regimens provided a potent and durable virologic response. Importantly, the patients started Kaletra after a median 30 months after virologic failure." My interpretation is that it is likely that the time

patients were maintained on a virologically failing regimen may have contributed to the success of Kaletra.

Does the success of Trizivir and Viread in patients with extensive resistance indicate as time on treatment progresses patients are easier to treat?

Another recent study shows that nucleoside resistance may not interfere much with the success of the quad regimen of AZT/3TC/Ziagen and Viread. [20]

A chart review of 116 people who switched to twice-daily Trizivir plus once-daily tenofovir found that most of them maintained or improved virologic suppression with the quadruple combination. After 3 to 301 weeks of follow-up (median 51 weeks), the primary investigator Dauer scanned records of everyone in the clinic who took Trizivir plus tenofovir for at least 24 weeks after another regimen. About half of them opted for the four nukes because of virologic failure of their current meds, and about half to dispel side effects or to start a more convenient regimen.

The study group had tried of median of 7 antiretrovirals over a median 6.6 years. The median lowest-ever CD4 count measured 91 cells/mm³, but before starting Trizivir/tenofovir the median count stood at 283 cells/mm³.

Thus the study population was clearly a patient population with viral disconnect at the time of initiation of the quad regimen. The lower baseline viral loads at the time of Trizivir/Viread initiation probably also contributed to the success of the regimen. These patients based on their viral loads also may have had significant amounts of HIV specific immunity contributing to their stability.

46 patients with three or more nucleoside patients had viral loads drop from 10,000 to 400 in 24 weeks. According to the authors, how many resistance mutations that patients in the cohort had did not affect their chances of a virologic response to Trizivir/Viread.

Median viral load fell from 400 copies/mL just before Trizivir/tenofovir to 87 copies/mL after 24 weeks of the quadruple collation. In that time the median CD4 count climbed to 315 cells/mm³.

Dauer discovered three factors that predicted failure to have a sub-400 viral load at week 24- 1. more antiretrovirals previously tried, 2. higher baseline viral load, and 3. a lower baseline CD4 count (Table).

The number of nucleoside resistance mutations a person had before starting Trizivir/tenofovir did not affect chances of virologic response in this cohort. Among 84 people with genotypic data on tap, the 46 with 3 or more nucleoside mutations before Trizivir/tenofovir enjoyed a median viral load drop from 10,000 to 400 copies/mL after 24 weeks of treatment.

Two thymidine analog mutations did, however, make virologic response less likely. Significantly fewer people who drove their viral load below 50 copies/mL had the T215Y/F mutation (P = 0.003) or T215Y/F plus L210W (P = 0.016).

My conclusion from this study are that less potent drugs such as drugs whose potency is limited by drug resistance are needed to treat this population. This suggests that drug resistance itself in some situations make it easier not harder to treat certain patients.

While this study doesn't prove that accumulating additional mutations makes patients easier to treat it certainly suggests it doesn't make it harder. This goes strongly against the notion that continuing virologically failing regimens risks progressive resistance that automatically jeopardizes patient's chances for future treatment.

Given what we are learning about the subtleties and complexities of drug resistance, I believe we should

re-evaluate the idea that achieving maximal viral suppression should be the main goal of treatment. Patients can often remain healthy and stable with ongoing viral replication and drug resistance. Again I believe the focus on treating healthier drug resistant patients should be as much on toxicity as maximal viral suppression.

In assessing the value of the treatment strategy of Trizivir and Viread it is important to consider that strategy in the context of the principles of therapy. Trizivir/Viread is usually a well tolerated and easy to adhere to regimen that in this patient population also spares the use of newer meds and preserves those meds as treatment options. In addition it doesn't seem to compromise future treatment options by causing increased clinically relevant cross resistance within the NRTI class of meds.

However, from a toxicity point of view, it requires continued AZT therapy that is a potential contributory factor to lipodystrophy progression.

If my hypothesis is correct that over time some patients become easier to treat than perhaps AZT could be stopped or there are other safer maintenance regimens that could be tried. There may be additional switch options for these patients that would enable them to stop or reduce AZT that can cause lipodystrophy.

As we expand our understanding of pathogenesis to include a sophisticated understanding of how HIV and the immune system interact in individual patients and over the course of treatment we may be able to make progress in improving the efficacy of treatment and reducing toxicity for many patients.

I believe that expanded understanding will include viral fitness, immune activation and HIV specific immune responses. Of course to fully utilize these principles we need tests that can monitor these parameters in individual patients the way we use the viral load test to assess drug potency or resistance testing to test for drug resistance

A report from my clinical practice of patients who are getting easier to treat over time.

Some of my most previously difficult to treat patients have had remarkable responses to regimens incorporating hydroxyurea. I presented a group of these patients at a seminar for the Immunology Department of Cornell Weill Medical College in 2005 [21] in which I reported the specific treatment histories of forty patients in whom HU was incorporated into their regimens. Prior to starting hydroxyurea these patients had received sequential therapy first with NRTI drugs before the availability of HAART and with protease inhibitors and NNRTI's after the advent of HAART. As a result of historical sequential therapy MDR-HIV developed and often was associated with clinical and immune failure as well as virologic failure.

These patients including had two or three class drug failure in the mid nineties after early HAART with low T cells and high viral loads. Now up to ten years later as their therapy has evolved with hydroxyurea consistently in the mix these same patients currently have high T helper cell counts, low to undetectable viral loads and good clinical health. Of great importance I believe is that some of these patients regimens have evolved to minimal and low toxic regimens. For example some patients are on combination regimens such as Ziagen, Efavir and a low dose of hydroxyurea. These patients are succeeding on the same or similar drugs to which they previously had failed despite remaining resistant according to genotype testing to the drugs they are taking.

In the parlance that I believe contains an important insight, these previously "difficult to treat" patients are now "easier to treat" patients. Easier to treat patients may require less therapy and less toxic therapy to succeed in achieving key treatment goals.

I believe it would be of great importance to better understand the mechanisms that account for the success of these patients and why they now appear easier to treat. My sense is that these outcomes are the result of a combination of factors involving perhaps several mechanisms of action of HU such as dampening immune activation or directly boosting the potency of certain nucleosides, as well as non HU

related factors such as the development of minor mutations discussed earlier or changes in viral fitness, or emerging HIV specific immunity.

But whatever the mechanism of actions are these patients or even whether in some patients it is even in part due to the use of hydroxyurea I believe these patients are a dramatic example of an important clinical phenomenon in which some patients on treatment with drug resistance are getting easier to treat over time. Easier to treat patients may benefit from different strategic approaches to treatment than more difficult to treat patients. For example minimizing drug toxicity can be more easily achieved in easier to treat patients that may improve clinical outcomes. In the developing world where access to treatment is restricted this distinction may help access and cost issues.

If we better understood why some patients are doing better and better with less and possibly less toxic therapy perhaps at some point we could devise treatment approaches to amplify this effect and allow some patients to evolve to no therapy at all.

I believe more research is needed into studying these patients immune responses which might even bear fruit in the search for a preventative and/or therapeutic vaccine. I call on my colleagues in the University labs, government sponsored institutions, foundations and drug companies to study these patients to understand better these observations from a clinician in longtime clinical practice.

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