

A new approach for 'deep salvage' trials in advanced HIV infection [OPINION]

AIDS:Volume 21(12)31 July 2007p 1503-1506

Lederman, Michael Ma; Miller, Veronicab; Weller, Ianc; Deeks, Steven Gd

>From the aCenter for AIDS Research, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio, USA

bForum for Collaborative HIV Research, The George Washington University Washington, DC, USA

cUniversity College London, London, UK

dUniversity of California, San Francisco, California, USA.

Abstract

One of the most difficult problems in HIV care today is the management of individuals infected with multidrug-resistant viruses. Well-controlled, carefully designed clinical trials have recently resulted in the approval of several new antiviral agents for the treatment of drug-resistant HIV. The design of these trials has come at the cost of the predictable emergence of drug-resistant viruses among individuals randomly assigned to receive a suboptimal revised treatment regimen. We propose here a different approach to the evaluation of drug efficacy in individuals harbouring multidrug-resistant HIV.

In recent years, a number of clinical trials have investigated the utility of new antiretroviral drugs for the treatment of drug-resistant HIV. These trials have led to the approval of several highly effective drugs, including enfuvirtide, tipranavir and darunavir [1-3]. Several other drugs are in active development and are likely to become widely available in the next few years [4,5]. The addition of these new agents is welcome, but their approvals come at a cost.

Most if not all of the current generation of 'salvage' studies are based on the model initially used for the development of enfuvirtide [2,3]. In those studies, individuals with multidrug-resistant HIV are randomly assigned to receive an 'optimized background' regimen with or without the addition of the new drug. Not surprisingly, many of the patients who feel the greatest need to enroll in these studies have very advanced disease and limited therapeutic options. In other words, such studies generally attract the most desperate, as those who are doing well immunologically have the option of waiting for the drug's safety and efficacy to be firmly established [6].

So what happens to desperate patients with highly resistant HIV who enroll in these 'salvage' studies? If the optimized background therapy regimen contains no agents with antiviral activity against the patient's virus population, then treatment failure is likely in either arm. In this scenario, those randomly assigned to the control arm (no new agent) are in essence recycling drugs that are not likely to be effective, whereas those randomly assigned to the experimental arm are being exposed to a regimen containing a single effective agent. As has been shown repeatedly, the use of a regimen containing only one fully effective agent is associated with a high risk of virological failure and the rapid emergence of a virus that is resistant to the new agent and potentially other agents within the same class [7,8]. If the optimized background regimen contains a single effective agent, and if the patient is randomly assigned to the control arm, then treatment failure is again likely. More importantly, the patient in this control arm will also probably lose an important future drug option. Finally, if there are two or more potentially effective agents in the background regimen, then the patient is likely to experience sustained virological control irrespective of the outcome of the randomization. In this instance, participation in the study may not help determine the contribution of the new agent's activity to the study's outcome.

The current paradigm for the rapid evaluation of novel antiretroviral drugs is thus dependent upon the enrollment of patients who are destined to fail the new treatment regimen. Many of these individuals have, by their treatment failure, contributed to the 'success' of the trial but at great cost to their own care. These individuals have been randomly assigned to receive a regimen that often contains a single new agent and as a result, their viruses have developed resistance to this agent, with potential long-term consequences. This use of 'sequential monotherapy' is one important reason why many patients with highly resistant virus are now presenting in clinics [9-11].

Most clinicians are well aware of this gut-wrenching dilemma. Given the advanced nature of their patients' disease and the slow pace of new drug development, they often have no choice but to roll the dice and hope for the best. There are, however, other possible approaches for drug development that should be considered [12,13], including unique randomization schemes that prevent exposure to effective monotherapy, or even single arm studies, as we outline below.

Largely as a result of the complex ethical issues involved in current salvage therapy studies, DeGruttola and colleagues [12] recently called for an end to treatment trials that enroll individuals to receive regimens that include only a single new drug. They proposed that only individuals with a potential of receiving two new drugs be randomly assigned to receive these new drugs or to receive a revised regimen that includes no new agents. Their proposal is a good start, as this approach will limit the harm associated with the application of an active drug monotherapy. We believe, however, that only a limited amount of efficacy data is accrued from the comparison of virological responses in individuals randomly assigned to receive two new drugs with the responses in individuals who are essentially 'recycling' drugs to which their viruses are already resistant. Also, the minimal antiviral response in the control arm may not be sufficiently different from the baseline levels of plasma viremia in either arm to justify the risks associated with randomization [2]. Although this risk might be attenuated by a crossover design that allows individuals in the control arm to receive the revised regimen containing the two new drugs after meeting prespecified failure criteria, this approach weakens the utility of the control arm as a comparator. This is particularly true because those rolling over to the experimental arm will not be a random sample, but rather a more advanced or sicker subset. Although comparisons can be made before the crossover, non-confounded comparisons between the two arms become difficult if not impossible after the rollover phase begins. As the approach outlined by De Gruttola and colleagues [12] will compare responses seen with two new drugs to responses seen with no new drug, and as the latter will be associated with a minimal change in HIV-RNA levels, a modification of this approach would be to perform a single arm study in which all subjects receive an optimal regimen, and the change from baseline becomes the primary outcome measure (see below).

Another modification of this approach would be to assign patients randomly whose virus is fully susceptible to at least two approved agents to receive an optimized regimen containing these two active drugs versus a regimen containing only one of these drugs plus the new agent under study. This study would be comparable with current treatment-naïve studies in which all patients are expected to do well; thus the endpoint could be non-inferiority. This approach has the advantages of randomization and also the assurance that all patients have a good chance of receiving an effective regimen. On the other hand, only a minority of individuals with advanced disease may be eligible for this kind of study as few have two or more fully effective drugs available to them. Also, such a study would need to be unblinded, and the incentive of those in the control arm to drop out after randomization would be great.

We would therefore like to propose an additional model for consideration. Whereas DeGruttola and colleagues [12] proposed randomization to a regimen containing either two effective drugs or no effective

drugs, we believe that a more efficient and safer approach is a single arm study in which all patients receive one new investigational drug and at least one established, well-characterized drug to which the patient's virus is fully susceptible.

How then would one define the contribution of the new investigational agent? There is now sufficient experience with most approved agents such that a phenotypic (and to a lesser degree genotypic) assay can be used to define, for each patient, which drugs in an optimized background regimen are fully active, partly active or not active. This is particularly true for the recent generation of drugs that are often used in salvage therapy [14,15]. The US Food and Drug Administration (FDA) now mandates that these phenotypic and genotypic susceptibility scores be defined during drug development. Also, there is now sufficient experience with each of these drugs such that a range of expected virological responses can be estimated when each drug is used with any number of fully effective drugs [16]. Single arm salvage trials testing a new experimental agent (e.g. agent E) in a regimen containing only one other fully active agent (e.g. agents A, B, C or D) can be evaluated in the light of previous responses to agents A, B, C or D, when each of those drugs had been used in a salvage regimen that contained one other active agent. A successful outcome of a salvage study of agent E, when used with a background regimen containing only one other effective agent (A, B, C or D), would be a treatment response that falls within the expected range.

This approach is illustrated in Table 1, in which the known response rates for approved drugs A, B, C and D when used in a regimen containing one and only one other fully effective drug are presented. As an example, when agent A was combined with either agents B, C or D, the response rates ranged between 70 and 85%. Therefore for trials of the new agent E, ranges of complete responses when used in combination with these other active agents should be between 70 and 85%. A failure to achieve such a response would suggest that the experimental agent is not as active as the other agents commonly used in patients with multidrug-resistant HIV. In that instance, additional studies would be necessary to define what role if any this drug might have as a component of salvage therapy.

The analysis outlined in Table 1 requires that there is sufficient clinical evidence with the 'background' drugs such that one can predict outcomes when these drugs are combined with a new fully effective agent (e.g. agent E). Table 1 assumes that the background regimen contains one and only one fully effective agent. Recent data, however, indicate that the more fully or partly active drugs in a regimen, the better the outcome [1,17-19]. Rather than excluding patients who may be able to construct regimens with more than one fully effective agent in their background regimen, an alternative approach would be to calculate a continuous phenotypic or genotypic susceptibility score for each subject's regimen, assuming that agent E is fully effective [15,17,18]. A regression analysis could then be performed to determine if the frequency of complete virological responses seen in the current study is consistent with that seen in previous studies (i.e. do the response rates in the current study fall within a range predicted by previous studies, after controlling for the background regimen's susceptibility score and perhaps other variables such as pretherapy CD4 T-cell count and viral load).

A less ideal option is to pursue the successful strategy used in the recent development of darunavir: perform one or two small randomized controlled studies aimed at precisely defining long-term virological activity, followed by larger non-randomized studies enrolling similarly defined patients aimed at confirming the original efficacy and safety outcomes [20]. Although this approach still involves the risk of randomization, it at least limits the number of subjects placed at risk and may thus represent a compromise between the needs of those evaluating these drugs (e.g. regulatory agencies, guideline panels, third-party payors) and the needs of the patients participating in the studies.

It should be noted that single arm studies of activity are routine for the study of new anticancer agents and have been used successfully to demonstrate good outcomes in pathogenesis-oriented HIV clinical trials [21,22]. Although as outlined above, evaluating the activity and safety of a single new antiretroviral drug is complicated by testing of the drug in combination regimens, we argue here that the contribution of the new drug of interest can be evaluated in the light of the baseline resistance testing and our growing experience in the treatment of infection with multidrug-resistant viruses. This approach has been useful in defining the activity of new agents used in salvage therapy [23]. Also, much of the data used for the recent FDA approval of the protease inhibitor darunavir came from a single-arm study (POWER 3) [20].

There are potential disadvantages to this strategy. The most important is that patients with no remaining options would be excluded from studies. Most clinicians and patient advocates will find this unacceptable, particularly for patients with very advanced disease who may not survive long enough to see the new drug formally approved. We believe that potentially active drugs can and should be provided for such patients through expanded access programmes as these agents are being developed. Also, we believe that such programmes should be at least partly funded by the sponsor with an aim of collecting data as rigorously as possible. Finally, we would advocate for allowing patients in this situation to combine experimental drugs whenever possible.

Another problem is that there is the potential of bias in the use of historical controls. Efforts must thus be made to account for recognizable biases when these studies are performed. The lack of randomization in a registrational study is not yet fully consistent with current approaches for drug approval used by the FDA and the European Medicines Agency. These agencies would need to accept the idea that a single arm study can demonstrate drug efficacy convincingly. We believe that such a compromise is feasible and reasonable because a drug's direct antiviral potency can be measured precisely in vivo in small cohorts of individuals over a 1-2 week period, and because the contribution of one drug to a combination regimen's long-term virological efficacy can be estimated if the activity of the other drugs is well characterized. We acknowledge, however, that the lack of a control arm will make it more challenging to evaluate short and long-term toxicities. As it is highly unlikely that the approval of any drug would be based on one single trial, these concerns could be addressed through additional single arm studies or randomized studies performed in a less-experienced patient population.

There are potential benefits to this strategy. First, there is a likelihood of benefit to all trial participants, rather than only to those fortunate enough to be randomly assigned to a regimen containing more than one effective agent. Also, because only a single arm is utilized, fewer subjects are needed to complete these studies. Finally, this approach avoids the bias that can be introduced by crossover designs.

On balance, we believe that there is enough information in the databases of the salvage trials that have already been completed to generate some confidence in the expected virological responses to combinations of new drugs used in salvage. What is more, as this and other newer strategies are implemented, the database will evolve with time and become more robust. Most importantly, however, we believe that a revision of our salvage trial strategies will allow for the timely development of new and useful salvage regimens without harming those volunteers whose participation is critical for their approval and in whose interests these agents are being developed.

References

1. Hicks CB, Cahn P, Cooper DA, Walmsley SL, Katlama C, Clotet B, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two

randomised open-label trials. *Lancet* 2006; 368:466-475.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

2. Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; 348:2175-2185.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

3. Lazzarin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348:2186-2195.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

4. DeJesus E, Berger D, Markowitz M, Cohen C, Hawkins T, Ruane P, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naive and treatment-experienced patients. *J Acquir Immune Defic Syndr* 2006; 43:1-5.

[[Fulltext Link](#)] [[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

5. Fatkenheuer G, Pozniak AL, Johnson MA, Plettenberg A, Staszewski S, Hoepelman AI, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Meds* 2005; 11:1170-1172.

[[Context Link](#)]

6. Deeks SG, Barbour JD, Martin JN, Swanson MS, Grant RM. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis* 2000; 181:946-953.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

7. Gulick RM, Hu XJ, Fiscus SA, Fletcher CV, Haubrich R, Cheng H, et al. Randomized study of saquinavir with ritonavir or nelfinavir together with delavirdine, adefovir, or both in human immunodeficiency virus-infected adults with virologic failure on indinavir: AIDS Clinical Trials Group Study 359. *J Infect Dis* 2000; 182:1375-1384.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

8. Hammer SM, Vaida F, Bennett KK, Holohan MK, Sheiner L, Eron JJ, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. *JAMA* 2002; 288:169-180.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

9. Deeks SG. Treatment of antiretroviral-drug-resistant HIV-1 infection. *Lancet* 2003; 362:2002-2011.

[[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

10. Ledergerber B, Lundgren JD, Walker AS, Sabin C, Justice A, Reiss P, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004; 364:51-62.

[[Medline Link](#)] [[Context Link](#)]

11. Richman DD, Morton SC, Wrin T, Hellmann N, Berry S, Shapiro MF, Bozzette SA. The prevalence of antiretroviral drug resistance in the United States. *AIDS* 2004; 18:1393-1401.

[[Fulltext Link](#)] [[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

12. De Gruttola V, Flexner C, Schapiro J, Hughes M, Van Der Laan M, Kuritzkes DR. Drug development strategies for salvage therapy: conflicts and solutions. *AIDS Res Hum Retroviruses* 2006; 22:1106-1109.

[[Context Link](#)]

13. Struble K, Murray J, Cheng B, Gegeny T, Miller V, Gulick R. Antiretroviral therapies for treatment-experienced patients: current status and research challenges. *AIDS* 2005; 19:747-756.

[[Fulltext Link](#)] [[Medline Link](#)] [[CrossRef](#)] [[Context Link](#)]

14. Baxter JD, Schapiro JM, Boucher CAB, Kohlbrenner VM, Hall DB, Scherer JR, Mayers DL. Genotypic changes in human immunodeficiency virus-1 protease associated with reduced susceptibility and virologic response to the protease inhibitor tipranavir. *J Virol* 2006; 80:10794-10801.

[[Context Link](#)]

15. Kempf DJ, Isaacson JD, King MS, Brun SC, Sylte J, Richards B, et al. Analysis of the virological response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-

infected patients receiving lopinavir/ritonavir therapy. *Antivir Ther* 2002; 7:165-174.

[\[Context Link\]](#)

16. Miralles D, Falcon R, Thommes J. Limited positive predictive value of resistance testing in treatment-experienced patients. *AIDS* 2005; 19:2178-2179.

[\[Fulltext Link\]](#) [\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)

17. Montaner J, Guimaraes D, Chung J, Gafoor Z, Salgo M, DeMasi R. Prognostic staging of extensively pretreated patients with advanced HIV-1 disease. *HIV Clin Trials* 2005; 6:281-290.

[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)

18. Swanstrom R, Bosch RJ, Katzenstein D, Cheng H, Jiang H, Hellmann N, et al. Weighted phenotypic susceptibility scores are predictive of the HIV-1 RNA response in protease inhibitor-experienced HIV-1-infected subjects. *J Infect Dis* 2004; 190:886-893.

[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)

19. Beatty G, Hunt P, Smith A, Hoh R, Huang W, Martin J, Deeks SG. A randomized pilot study comparing combination therapy plus enfuvirtide versus a treatment interruption followed by combination therapy plus enfuvirtide. *Antivir Ther* 2006; 11:315-319.

[\[Medline Link\]](#) [\[Context Link\]](#)

20. Preziata (darunavir) package insert. East Bridgewater, NJ: Tibotec Therapeutics; July 2006.

[\[Context Link\]](#)

21. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997; 277:112-116.

[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)

22. Lederman MM, Connick E, Landay A, Kuritzkes DR, Spritzler J, St Clair M, et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315. *J Infect Dis* 1998; 178:70-79.

[\[Medline Link\]](#) [\[Context Link\]](#)

23. Benson CA, Deeks SG, Brun SC, Gulick RM, Eron JJ, Kessler HA, et al. Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients. *J Infect Dis* 2002; 185:599-607.