

Drug Development Strategies for Salvage Therapy: Conflicts and Solutions

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INTRODUCTION

WIDESPREAD USE OF ANTIRETROVIRAL DRUGS has led to an increasing prevalence of multidrug-resistant HIV-1 infection, and development of effective treatments for patients with such infections should be a public health priority.¹ As recent registrational studies demonstrate, there are often perceived conflicts between the goals of drug development (determining the safety and efficacy of a new drug) and those of clinical practice (providing the most rapid possible access to effective drug combinations). We focus much of our discussion on these studies, as pharmaceutical companies drive much of the current research agenda and can largely specify how they would like their agents to be tested. Conflicts may be reduced, though not entirely eliminated, when studies are sponsored by disinterested third parties. Conflicts between the needs of study participants and the goals of drug development are particularly noteworthy in settings where resistance to one or more drugs in a multidrug regimen can occur.

To address the apparent conflicts between the needs of study participants and pharmaceutical manufacturers, we propose changes in current research strategies, summarized as follows. (1) Salvage studies should be designed to minimize the chance that the study participants receive only one active drug. New drugs must be developed in conjunction with other new or existing drugs to create potent regimens; relevant information about how best to combine drugs should be developed early in phase II investigations. (2) Study participants should be maintained on assigned regimens long enough to provide reliable comparisons of toxicity between the new and standard treatments. When crossover to the new regimen is allowed, appropriate methods must be used to adjust for the resulting informative censoring as well as for uncontrolled use of potent drugs. (3) The primary endpoint in salvage studies of antiviral drugs should generally be suppression of virus below levels of detection. (4) Because drug

efficacy depends on the genotype of the microbe or cell, studies must provide adequate information for classifying future patients according to their predicted response to therapy. (5) The regulatory policy must be modified to ensure proper review of drugs that are targeted to patients according to genotype of the infecting agents.

STUDY DESIGN

In TORO^{2,3} and RESIST, two landmark studies of new salvage treatments for HIV-1 infection, a single drug, enfuvirtide (ENF) or tipranavir (TPV), was added to optimized background regimen (OBR) and compared to a standard-of-care (SOC) arm. Study participants who failed treatment on the SOC arm were crossed over to the new drug. The shortcomings of this approach include the following. (1) Participants for whom there are no active drugs in the OBR may essentially be receiving monotherapy, and therefore be at high risk of treatment failure and development of additional resistance. (2) Rapid crossover to the new drug prevents long-term toxicity comparisons. (3) Differential use of potent drugs other than the study drug may induce a bias in favor of the new drug, especially in unblinded studies. In RESIST, study participants were asked to decide prior to randomization whether or not to include ENF in their OBR. While full compliance with this decision would result in balanced randomization, there was less actual use of ENF in the SOC arm. Because failing study participants could cross over to TPV at 8 weeks, some who were randomized to SOC might have sabotaged their regimens by failing to take ENF; doing so would have allowed them to avoid exposure to ENF as their only active drug. Similarly those randomized to TPV might have reconsidered their refusal of ENF to avoid effectively receiving TPV monotherapy. These considerations underscore the potential for conflict between study protocol and good clinical practice.

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The choice of endpoint—achievement of at least a 1-log drop in RNA at week 24—also raises concerns about the interpretability of the RESIST study. This endpoint has not been clinically validated in this setting, and the choice of a low bar for success may reflect concerns about the shortcomings of effective monotherapy. While transient reductions in viral load were associated with short-term clinical benefits in the era of mono or dual-nucleoside therapy, longer-term benefits of such reductions have not been established in the current era. Study participants with short-term RNA reductions may develop resistance mutations that reduce future drug options and thereby experience negative long-term consequences that outweigh short-term gains. Even in the prior era, reductions in viral load were found to be at best only moderately good surrogates.⁴

We propose that patients not be included in salvage studies if they effectively will be receiving monotherapy. Study participants without access to a currently licensed active drug to combine with the study drug should receive two new drugs. This requirement may exclude from studies many patients in need of a new drug, but most of them will benefit from waiting for access to another drug with which to create a potent regimen. For those who cannot wait, compassionate use programs may provide early access. As an alternative to the RESIST design, we propose the following. Participants with no active drug besides ENF are randomized to TPV + ENF vs. SOC without ENF; those who have another active drug are randomized to TPV + OBR vs. SOC. Patients who refuse ENF but have no other active drug would either be excluded from participation or included in a special stratum and randomized to TPV + OBR vs. SOC. The advantages of this design are that no participant willing to take ENF gets effective monotherapy, and that the endpoint can be viral suppression below detection. The impact of TPV alone on toxicity and efficacy can be evaluated among participants who refuse ENF. Offsetting the apparent disadvantage of studying TPV only in combination with ENF in certain types of patients is the fact that this use of TPV may be optimal for such patients. We can replace ENF in this example with any drug never before seen by the patient population, whether new or not. Although studying one drug only in combination with another may not be optimal from the perspective of drug development, it may best meet the interest of potential study participants.

Often an incentive for patients to enter a study is access to the new drug after failing the SOC arm. When crossover occurs early—8 weeks in RESIST and 12 weeks in TORO—there is little information on which to base 24- and 48-week toxicity comparisons because patients at highest risk of toxicities may have a short experience on the SOC arm. Moreover, participants may be crossed over before there is any real evidence of the benefit of doing so. Crossover designs should be used only when there are no effective therapeutics available to participants receiving SOC, and crossover should be delayed as long as possible. Phase II data on genetic barrier and rate of resistance selection for new drugs can help in designing appropriate criteria for crossing over. These criteria must be drug specific, as considerations for older drugs may not be relevant to new classes of inhibitors. Criteria for crossover based on CD4 T-lymphocyte count may be preferable to those based on viral load, because such criteria better reflect the risk of clinical progression for advanced patients.⁵

Adjusting for bias

Crossover studies can yield biased results because factors that influence crossover may also influence risk of toxicity, and differential use of potent treatments between arms can affect the interpretability results of these studies. To determine whether differential use of ENF was responsible for the apparent superiority of the TPV treatment arm in RESIST, analyses conducted by the FDA were stratified by actual (not intended) use of ENF. Such analyses suffer from confounding by indication; i.e., the choice of treatment may depend on factors that impact the risk of outcome. Only analyses that take this phenomenon into account can provide valid estimates of the effect of TPV adjusted for actual ENF use. These methods adjust for known confounding factors by (1) estimating the probability that a study participant used ENF, given his or her personal characteristics; (2) regressing the study endpoints on treatment and patient characteristics; and (3) combining these analyses to estimate the TPV effect.^{6,7} Methods to reduce the dependency of model assumptions and to analyze sensitivity to unmeasured confounding factors are also available.^{8,9} These methods also permit valid estimation of the risk of toxicity from crossover studies, correcting for the bias that results from analyzing only study participants who remain on assigned therapy. Furthermore, these methods permit use of information on toxicity obtained after crossover to the new drug.

Use of phase II information

Requiring that all participants in phase III studies receive two new drugs makes it difficult to estimate the activity of either alone. Therefore, more information about activity and resistance must be developed from phase II studies. In addition, investigation of combinations of new drugs (including pharmacokinetic studies undertaken in healthy volunteers) must be done earlier in phase II; this is an important role for federally funded clinical research programs. In some cases, factorial designs are useful for finding the most promising drug combinations. If these studies are short enough to keep the onset of resistance low, factorial designs that involve monotherapy (or effective monotherapy) may be appropriate. Frequent measurements of disease burden, such as HIV-1 RNA, would not only facilitate determination of drug activity, but also provide a safeguard against development of resistance by allowing rapid detection of viral rebound, upon which the drug can be stopped.

Resistance classes

Roberts and Chabner¹⁰ recommended that FDA fasttrack programs promote more selective use of targeted cancer drugs, and proposed a new FDA approval mechanism that would require sponsors to identify subgroups of patients likely to benefit from these drugs. They further recommend that such studies begin in the earliest phases of development, and that the FDA negotiate commitments to conduct appropriate phase 4 studies. Such recommendations also apply to drugs targeting resistant strains of HIV-1 and other infectious agents. For example, in RESIST, TPV was shown to be effective against some, but not all, patterns of PI resistance mutations; hence the

need to identify classes of patients expected to benefit from TPV. Defining such classes requires more than simply demonstrating that some score (like number of PI mutations) predicts outcome. Balancing costs and benefits requires estimating the probability of response by class and the probability of toxicity based on baseline factors. Designing studies to produce such information impacts not only study size but also inclusion/exclusion criteria, like resistance profile, and the presence of coinfection or of other medical conditions. There must be a balance between excluding patients who are likely to be resistant to the drug (as was done in RESIST) and recruiting a heterogeneous population with a large spectrum of resistance patterns to facilitate prediction of resistance. Failing to screen for a rare resistance pattern that compromises the drug could effectively expose some patients to monotherapy; but the more patients excluded, the fewer the patterns available for analysis.

DISCUSSION

Ethical considerations

For any clinical research study, physicians can only ethically enroll patients when they believe that such enrollment is in the best interest of the patient. Conflicts of interest can arise when physicians derive income (e.g., support for personal or staff salary or professional status) from enrolling a patient into a salvage therapy study, but the study design does not conform to their current standard of practice. Belief that the study may benefit patients in the future does not justify enrollment of patients who, in the physician's opinion, do not stand to benefit or may even be harmed by the study. Our recommendations are developed specifically to reduce the number and degree of such conflicts in the future.

Current research agenda

There are currently under development both new classes of drugs, such CCR5 inhibitors, and drugs from existing classes with novel resistance patterns; every drug poses some special concerns. Because CCR5 inhibitors may induce a tropism shift with negative long-term clinical consequences, the need for partnering these drugs with other potent agents is particularly acute. Full virologic suppression at 48 weeks is the most relevant endpoint in studying CCR5 inhibitors; and proper study of its effect on tropism shift requires avoidance of premature crossover. Study of drugs from existing classes requires identifying patient populations likely to be sensitive to the new drug and to one other potent agent, but not to existing drugs from the same class.

Our recommendations will be challenging to implement. Partnering drugs requires cooperation across pharmaceutical companies and may impact labeling. Rapid crossover to a new study drug is used as an inducement to enrollment, even when it compromises the usefulness and validity of studies. Broadening the use of sophisticated methods for bias adjustment requires resources and training. Meeting these challenges will require collaborative ties among investigators and statisticians in industry, government, and academia. In a recent report, the FDA noted the following: "There is currently an urgent need for additional public-private collaborative work on applying technologies such as genomics, proteomics, bioinformatics systems,

and new imaging technologies to the science of medical product development." Only by making resources available for such collaboration can drugs targeted to diverse multidrug-resistant viruses be developed and used in an optimal way.

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REFERENCES

1. Stubble K, Marray J, Cheng B, Gegey T, Miller V, and Gulick R: Antiretroviral therapies for treatment-experienced patients: Current status and research challenges. *AIDS* 2005;19:747-756.
2. Lalezari JP, Henry K, O'Hearn, *et al.*: for the TORO 1 Study Group. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003;348(22):2175-2185.
3. Lazzarin A, Clotet B, Cooper D, *et al.*: for the TORO 2 Study Group. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003;348(22):2186-2195.
4. HIV-1 Surrogate Marker Collaborative Group: Human immunodeficiency virus type I RNA level and CD4 count as prognostic markers and surrogate end points, *AIDS Res Hum retroviruses* 2000;16(12):1123-1133.
5. Loutfy M, Walmsley S, Mullin C, Perez G, and Neaton J: CD4+ cell count increase predicts clinical benefits in patients with advanced HIV-1 disease and persistent viremia after 1 year of combination antiretroviral therapy. *J Infect Dis* 2005;192:1407-1411.
6. Robins JM: Marginal structural models versus structural nested models as tools for causal inference. In: *Statistical Models in Epidemiology: The Environment and Clinical Trials* (Halloran ME and Berry D, eds.), IMA Volume 116. Springer-Verlag, New York, 1999, pp. 95-134.
7. Robins JM: Robust estimation in sequentially ignorable missing data and causal inference models. In: *Proceedings of the American Statistical Association. Section on Bayesian Statistical Science*, 1999, pp. 6-10, 2000.

8. Wang Y and van der Laan MJ: Data adaptive estimation of the treatment specific mean. UC Berkeley, Division of Biostatistics Working Paper series, Working Paper 159, 2004, <http://www.bepress.com/ucbbiostat/paper159>.
9. van der Laan MJ and Robins JM: *Unified Methods for Censored Longitudinal Data and Causality*. Springer-Verlag, New York, 2003.
10. Roberts T and Chabner B: Beyond Fast track for drug approvals. *New Engl J Med* 2004;351:5.

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