



Proof of concept studies/translational research; new hypotheses

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

By Bob Huff

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

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

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

rapidity of the viral load reduction (or the steepness of the slope) could be a secondary indicator of the drug's activity.

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

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

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

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

Although small numbers of patients are involved at this stage of drug development, there are significant concerns associated with exposing salvage

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

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

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

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