Is There a Best Regimen for Initial Antiretroviral Therapy?

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First of all, it is important to know what exactly is meant by “the best.”

Since zidovudine became the first FDA-approved antiretroviral agent in 1987, an additional 25 antiretrovirals have been approved, as well as a number of fixed-dose, coformulated, multidrug combination products for the treatment of HIV infection. As a result of combination antiretroviral therapy (cART), HIV infection has become a manageable chronic condition, with a life expectancy in North America and Western Europe approaching that of uninfected persons.

Various guidelines exist to help clinicians choose initial cART. For instance, the US Department of Health and Human Services (DHHS) Guidelines list a number of “preferred” and “alternative” drugs or drug combinations, and references the studies that support these recommendations. The guidelines also list advantages and disadvantages of various combinations. Nevertheless, no single combination is noted as “the best” by any of the published guidelines.

So, is it possible to determine a single best combination, or perhaps 2 or 3 equally good combinations? If so, why hasn’t it been done? Finally, does it really matter if we determine the top 1 to 3 combinations, when the 7 combinations listed by the DHHS Guidelines as preferred all seem to work quite well?

It seems to me that many patients want to know the answer. Patients frequently ask that I start them on the “best” combination. Or, they ask what I would take if I were starting antiretroviral therapy myself (both patients and health care providers ask this). Thus, the question seems to be worth trying to answer, even if doing so turns out to be futile.

What is “best”?

First of all, it is important to know what exactly is meant by “the best.” We get there by asking more questions. Is it the combination that is tolerated by the greatest number of individuals, or the combination that has been shown to have the fewest adverse side effects at 1 year (or year 2, 3, 5, or more?) Or, does best refer to virologic potency (maximal suppression of HIV RNA)? Or to immunologic potency (increases in CD4+ lymphocyte counts)? What is the trade-off between potency and tolerability? What about dosing convenience (eg, one pill once daily vs. several pills once or twice daily)? And how does one balance the potential for rare but very serious side effects with more common but less serious side effects in our quest for the best regimen? Finally, is it possible that there is a different “best” combination for women than for men? Or for blacks than for whites?

All of these questions form the basis for clinical trial comparisons of different regimens. Of course, it is practically impossible to compare every feasible 3-drug combination (all 2600 of them), especially with new antiretrovirals being introduced at the rate of about 1 per year. And, after more than 2 decades of experience with cART we know that certain drugs shouldn’t be combined, and that certain combinations seem to work less well than others. So, perhaps the place to start would be to try to determine which of the seven combinations listed as “preferred” by the DHHS Guidelines is the best.

Many trials have been completed (often sponsored by the pharmaceutical industry) that compare one of these seven with another one of the seven. Typically, these trials involve about 300 participants in each of the two arms, and the trial is powered to show non-inferiority (typically this term means one regimen is not more than 10% worse and not more than 10% better than the other regimen). Occasionally, one combination is shown to be statistically superior to another, which would suggest that we may be getting closer to finding the elusive best regimen. However, many of the inferior regimens are found to be inferior because just a few (10 to 20) more participants in the
inferior arm compared to the superior arm stopped taking the combination for reasons related to tolerability. In other words, for the more than 95% of study participants who did tolerate the inferior combination, potency (ie, viral suppression to <50 copies/mL) was as good as it was in the superior combination.

Here is what we know so far:

1. Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are as good as, but no better than, protease inhibitor (PI)-based regimens, based on clinical and immunologic outcomes. In that same study, a three-class regimen (NNRTI + PI + NRTI) was not any better clinically or immunologically than either of the two-class regimens, and was associated with more toxicity. At least one meta-analysis of PI- and NNRTI-based trials is ongoing to determine if either of these two classes is associated with greater virologic suppression or immunologic benefit.

2. Two preferred integrase strand transfer inhibitor-based regimens (INSTI; raltegravir; elvitegravir) were found to be non-inferior to a preferred NNRTI-based regimen (separate and multiple trials); a third preferred INSTI-based regimen (dolutegravir) was found to be superior to the same preferred NNRTI-based regimen (as a result primarily of less toxicity in the dolutegravir arm), and non-inferior to another preferred INSTI-based regimen. Logically, an INSTI-based regimen found to be non-inferior to another INSTI-based regimen, which itself was found to be non-inferior to an NNRTI-based regimen, should not have been shown to be superior to the same NNRTI-based regimen. However, comparisons among separate trials cannot be made (except as part of a meta-analysis), because populations differ, circumstances differ, etc.

So, for now, we are left with having to choose from seven DHHS-preferred regimens (and a number of alternative regimens), all of which seem reasonably good. We may learn more when the results of Aids Clinical Trial Group (ACTG) 5257 are released in about 3 to 4 months; that study is a comparison of three of the seven DHHS preferred regimens: each of the two preferred PI-based regimens and one of the preferred INSTI-based regimens (raltegravir). ACTG 5257 enrolled more than 1800 participants; a seven-arm trial would likely require 7000 participants. In addition, the ACTG has publicly stated that ACTG 5257 will be the last, large, antiretroviral comparison it plans to do for the foreseeable future, focusing the group's resources instead on finding a cure. That leaves the marketplace, and post-marketing, industry-sponsored trials, to sort things out.

For now, it seems safest to conclude that, for an individual patient, the “best” regimen is the one from the DHHS preferred or alternative lists, that is taken 100% of the time.

References


