Do Studies Accurately Predict Treatment Effectiveness in the Real World?

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Clinical trials of HIV treatments have historically yielded more favorable results than those seen in the real world, a phenomenon known as the "trial effect" that has now been proved by researchers at the University of North Carolina (UNC) at Chapel Hill, according to an analysis published July 13 in the online journal *PLoS One*.

Though the researchers warn that this trial effect should be considered when interpreting the applicability of study results, they also stress that the divergence between clinical trial and real-world outcomes was seen in the early years of combination antiretroviral (ARV) therapy. More recent real-world experiences, involving treatments that are easier to take and associated with fewer side effects, often mirror the outcomes seen in clinical trials.

According to the UNC study authors, led by Prema Menezes, PhD, trial effect is an umbrella term for the benefit experienced by study participants simply by virtue of their participating in the trial. It includes the benefit of newer and more effective treatments, the way those treatments are delivered, increased care and follow-up, and the patients' own behavior change as a result of being under observation.

Trial effect, however, is notoriously difficult to test, especially during or immediately after studies are conducted, in the absence of real-world data to serve as comparisons.

To explore this, Menezes's group compared rates of viral suppression—the percentage of patients with undetectable viral loads—among patients who began ARV treatment in a clinical trial with patients who received ARV therapy through the UNC Hospital Infectious Disease clinic in two different time periods: 1996 to 1999 and 2000 to 2006.
Overall, 78 percent of patients achieved virologic suppression. However, trial participants were 16 percent more likely to achieve virologic suppression when compared with those receiving routine care through the UNC clinic.

The magnitude of this difference depended on the period in which ARV treatment was initiated. In the early period, trial participants were 42 percent more likely to achieve undetectable viral loads compared with non-trial participants. Although a difference was also observed in the more modern

period—a 7 percent increase in the likelihood of achieving undetectable viral loads—it was not statistically significant, meaning it could have been due to chance.

After adjusting the data to account for age, distance traveled to receive care at UNC ID clinic, pre-treatment viral loads, pre-treatment CD4 cell counts, months from HIV diagnosis to ARV treatment initiation, kidney function and the actual treatment regimens used—all of which can affect outcomes while on therapy—trial participants remained more likely to achieve virologic suppression than non-trial participants in the early period. By contrast, in the more recent period, virologic suppression of trial and non-trial participants was similar.

There may be several reasons why a trial effect was readily apparent in the early treatment period, the authors suggest. Improvements in ARV therapy—fewer pills and fewer side effects—and the change in attitude to HIV, which has come to be seen by many as a chronic, but treatable infection, may be among the explanations for the lack of demonstrable trial effect in the later period.

“In summary, we demonstrated, for the first time, that participation in HIV clinical trials resulted in an improved outcome compared to clinic-based treatment (i.e. trial effect), in ARV treatment naive patients drawn from the same population, even after controlling for multiple potential confounders,” Menezes’s group writes.

While these findings underscore the need to interpret clinical trial results carefully when considering their real-world applicability, Menezes and her colleagues seem encouraged by the more contemporary overlaps in efficacy rates. “The fact that no trial effect was observed in the current [ARV treatment] period argues that the efficacy demonstrated in clinical trials is likely to predict the effectiveness of the therapy in broader treatment populations,” her team writes. “Clinicians and public health officials may have increased confidence that treatment guidelines based on clinical trial data are relevant to routine clinical care.”

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