Is It Safe to Interrupt HIV Treatment During Cure Studies?

Previous research has shown that long interruptions are not safe—but what about shorter, more closely monitored gaps in treatment?

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In 2006, the pivotal SMART study threw the HIV community for a loop when it proved that "drug holidays," then in vogue as a means of escaping the side effects of antiretrovirals (ARVs), were in fact harmful to health.

Given those findings, it may seem counterintuitive that today it is common for researchers to take people with HIV off their ARVs during cure studies. Would this not also compromise their health, even if these treatment interruptions are shorter and more closely monitored than those studied by the SMART investigators?

Seeking to address concerns about adverse health events associated with what are known as analytical treatment interruptions (ATIs) in cure studies, a team of German investigators conducted a systematic review and meta-analysis of numerous studies in which investigators put people with HIV through either ATIs or the more loosely monitored structured treatment interruptions (STIs) that the SMART study's findings ultimately drove out of practice.

Cure studies use ATIs as a means of assessing how an investigational therapy affects the virus outside of the context of suppressive therapy. During participants' time off ARVs, investigators can measure how treatment affects the amount of time before the virus rebounds, the peak viral load, the ultimate viral load plateau and other factors.

Jörg Janne Vehreschild, PhD, of the department of internal medicine at the University Hospital of Cologne in Germany, led the team behind the new analysis, which was published in Clinical Infectious Diseases. He and his colleagues identified over 1,000 studies published through May 2017 that reported on adverse events among people with HIV during treatment interruptions, including STIs and ATIs.

The studies included in the analysis needed to describe the design of their treatment interruption, the frequency of CD4 count or viral load monitoring, the data covering the periods both before and after treatment interruptions, the previous time participants had spent on ARVs and various clinical outcomes, such as adverse health events, AIDS-related diseases and drug resistance.

Vehreschild and his colleagues narrowed down the list to 22 reports published between 1999 and 2016, including the SMART study, that included a cumulative 7,104 participants. Some studies restarted treatment after a pre-set period of time, while others did so based on changes in participants' CD4s or viral load. Ten of the studies were randomized controlled trials, seven were prospective studies that did not have a control group and that studied a particular intervention, and five were observational studies. Overall, these studies provided evidence that the new analysis' authors considered to be of moderate certainty.

These studies included participant groups that ranged between six and 5,472 people. The treatment interruptions lasted between seven days and 27 months. The frequency of viral load testing during these interruptions ranged between once every two days to every three months. Participants spent a median of 12 months on ARVs prior to their treatment interruption—between a median of three and 56 months, depending on the study.

The paper's authors divided the studies into various subcategories. Those with a maximum monitoring period of 14 days were considered narrow follow-up studies; the others fell into the wide follow-up category. Studies that had a maximum treatment interruption interval of more than four weeks were considered long treatment-interruption studies while the others were in the short treatment-interruption category.

Vehreschild and his coauthors used a broad definition of adverse events that included ARV drug resistance, severe adverse health events, HIV disease progression and death.

Overall, 3% of the pool of participants in the studies analyzed experienced any of these adverse events. This proportion was higher, at 3%, in the long treatment-interruption studies compared with the short treatment-interruption studies, in which 2% experienced adverse events. The highest rates of adverse events occurred among those who started their study with a CD4 count of 350 to 500 and those in a wide follow-up study—11% of participants in both categories experienced such negative outcomes.

Looking just at studies with long treatment interruptions, the authors found that zero percent of participants in studies with narrow follow-up intervals experienced adverse events, compared with 6% of those in studies with wide follow-up intervals. Further, zero percent of those in observational and uncontrolled interventional studies experienced adverse events, compared with 8% of those in randomized controlled studies. None of those who had an initial CD4 count greater than 500 experienced adverse events, compared with 6% of those with a CD4 count below 350 and 17% of those with a CD4 count between 350 and 500.

Across all studies included in the analysis, 3% of the pooled population of participants developed drug resistance while off ARVs, with 9% doing so in the wide follow-up interval studies and zero percent doing so in the narrow follow-up interval studies. In the randomized controlled trials, 6% developed drug resistance, compared with zero percent in the uncontrolled interventional studies. Zero percent of those with a baseline viral load above 500 experienced drug resistance, compared with 7% of those with a CD4 count between 350 and 500 and 16% of those with CD4s below 350.

In the studies with long follow-up intervals, 3% of participants experienced disease progression, including 5% of those in randomized controlled trials and 1% of those in observational and uncontrolled interventional studies. Eight percent of those with a baseline CD4 count of 350 to 500 saw their HIV disease progress, compared with zero percent of those with initial CD4 counts greater than 500.

Deaths were rare in these studies, with 1% of those in the randomized controlled trials and zero percent of those in the other types of studies dying during the follow-up period. Further, zero percent of those with more than 500 CD4s died, compared with 2% of those with 350 to 500 CD4s.

Pooling the 6,430 participants from the nine randomized controlled trials, the investigators compared those who stayed on ARVs throughout their study participation with those who were put through a treatment interruption. They found that interrupting treatment was associated with a 27% increase in the rate of adverse events. In the studies in which participants took ARVs for at least 24 months before enrollment, interrupting treatment was tied to a 2.75-fold increased risk of adverse events, compared with a 3.14-fold increased risk in studies in which participants took ARVs for 12 or fewer months prior to enrollment.

The authors of the analysis determined that there were associations between the overall proportion of adverse events during treatment interruptions and baseline CD4 count, baseline viral load and study type. After adjusting the data to account for various differences between the participants and studies, the authors found that longer follow-up intervals and having a baseline CD4 count between 350 and 500 were each associated with a higher rate of adverse events.

“Our systematic review and meta-analysis highlights an existing knowledge gap that has not been conclusively answered by previous landmark trials,” the study authors concluded. “Although these trials, most notably the [SMART study], showed an increased risk of [sickness] and mortality during [treatment interruption] compared to individuals who continued therapy, other, mostly small studies, with narrow follow-up intervals, suggested that patients with a [baseline CD4 count of greater than 500] and an undetectable viral load can interrupt therapy safely, if monitored frequently. From a clinical point of view, ATI seems not to bear a marked risk of [adverse events] or resistance.”

Addressing the delicate ethical balance that scientists must observe when designing HIV cure studies that include ATIs, the paper’s authors concluded: “The residual risk of disease progression or development of drug resistance mutation has to be balanced against the potential new insights or clinical benefits of experimental strategies including TI.”

The paper notes a lack of reports of people transmitting HIV during ATIs. However, a report published too recently to make it into this new analysis tells of an HIV-positive French man who went through an ATI in a cure study and transmitted the virus to his female partner. The case study suggested that the man’s untreated depression might have influenced his transmission risk.

A potential lesson learned from this couple’s experience was that cure researchers should be more mindful of screening study participants for factors that may compromise their capacity to mitigate

their risk of transmitting HIV while they either have or run the risk of having a detectable viral load during an ATI. In addition, investigators may recommend pre-exposure prophylaxis (PrEP) for the HIV-negative partners of study participants going through ATIs.
