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# Commentary: Indirect comparisons: a novel approach to assessing the effect of anti-HIV drugs

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The need to evaluate rapidly and provide access to anti-HIV drugs led, in 1997, to an expedited drug approval process, based on short term trials using viral load and CD4 cell counts as surrogate end points for clinical AIDS. The evidence for efficacy of many drugs is therefore based solely on trials using such end points, but it is useful to evaluate studies using clinical end points where available.

Yazdanpanah and coworkers used an indirect comparison of clinical outcomes from randomised controlled trials to compare the effects of drugs from either the protease inhibitor or the non-nucleoside reverse transcriptase inhibitor (NNRTI) class with two nucleoside reverse transcriptase inhibitors (nucleosides).[1] This approach introduces a novel concept to improve further our understanding of the relative efficacy of the two classes. This review suggests a better efficacy of the protease inhibitors than the NNRTIs.

It is important to understand the context of the results to draw conclusions relevant to today. Most of the randomised controlled trials focused on viral end points and were not designed to capture clinical events after virological failure.[2] Also, many of the drugs from the NNRTI and protease inhibitor classes are considered obsolete, although the NNRTI drug most represented, nevirapine, is still widely used. Furthermore, most trials were based on people with previous exposure to nucleosides and thus likely to harbour virus with resistance to the nucleosides at enrolment. Since the genetic barrier for NNRTIs is lower than for protease inhibitors (with a single nucleotide mutation sufficient to create resistance), it would be predicted that resistance would develop more rapidly with NNRTI based regimens than with protease inhibitor based regimens in this situation, and hence that the clinical outcome would be poorer. The review seems to confirm this prediction, finding little beneficial effect of NNRTIs at all. Importantly, the results for viral load and clinical outcomes are broadly consistent with a better effect of protease inhibitors. In patients starting anti-HIV therapy for the first time, however, several randomised controlled trials with surrogate end points have directly shown that the efficacy of NNRTIs is comparable and perhaps even superior to protease inhibitors.[3–5]

None the less, there are situations in which the findings of Yazdanpanah and coworkers are relevant to today.[1] Frequently, exclusive resistance to nucleosides is seen at failure of current regimens, including triple nucleoside regimens. Furthermore, the WHO has recently launched its 3 by 5 motto of providing anti-HIV therapy to 3 million people by the end of 2005. Hopefully, the therapy will be state of the art, but some may receive inferior regimens of 1-2 nucleosides, increasing the number of patients with resistance to these drugs. It will be critical to start randomised controlled trials with clinical outcomes to establish a rational order of utilisation of the available anti-HIV drugs in this situation. Hopefully, the WHO or other organisations will ensure that this critical knowledge is generated. Yazdanpanah and coworkers provide a strong rationale that this is important.[1]

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