Published in final edited form as:

Arch Intern Med. 2010 January 11; 170(1): 109–110. doi:10.1001/archinternmed.2009.459.

DAART for Human Immunodeficiency Virus–Infected Patients: Studying Subjects Not at Risk for Nonadherence and Use of Untested Interventions

Frederick L. Altice, MD and Sandra A. Springer, MD

Gross et al¹ reported no benefit from directly administered antiretroviral therapy (DAART) among antiretroviral-naïve patients enrolled in a randomized controlled trial (RCT). They should be commended for using the rigors of an RCT, yet serious concerns remain in their choice of study population and use of an untested DAART intervention.

The use of a single regimen, testing the durability of DAART, monitoring adherence using Medication Event Monitoring System (MEMS) caps (Aardex Corp, Zug, Switzerland), and examining genotypic resistance are major strengths of this trial. Highly motivated, antiretroviral-naïve subjects enrolled in clinical trials are probably the least likely population, however, to benefit from an adherence intervention. Correlates of problematic adherence (eg, active drug use, untreated mental illness, prior antiretroviral experience, and cognitive impairment) were known long before subject accrual.² Why, then, were they studied? After considerable costs to patients and taxpayers, we learned what we already knew from previous RCTs—DAART is not effective among subjects without predictors of nonadherence,³ while others benefit greatly.^{4,5} Arguably, DAART patients were not harmed. All of them, however, were potentially inconvenienced, and one-third reported the intervention not to be helpful. With increasing recognition of costs, it is highly unlikely that costly DAART interventions would ever be considered for this group. Moreover, this study was undertaken in an idealized fashion, with a highly selected group of patients, with little attention given to ensure that the results are applicable in real-world settings.

Potentially contributing to the lack of efficacy by DAART is the lack of selection of a DAART intervention with any proven efficacy. To demonstrate “proof of concept,” the DAART intervention should have been tested for safety and efficacy in phase 1 and 2 trials. In this case, the DAART intervention using health care providers was not previously studied nor do we know the fidelity to which the intervention protocol was followed.

Even if one remained convinced that DAART needed to be evaluated in this population, questions remain about the analytical approach. First, no preliminary data about the DAART intervention were available to guide the prespecified selection of a 0.075 difference between the 2 groups for the primary outcome. Second, clinical trials of antiretroviral-naïve subjects nearly always result in extremely high levels of nondetectable HIV-1 RNA levels, with little margin for improvement even if a proven adherence intervention were used. Such a ceiling effect allowed little room for improvement.

Notwithstanding these limitations, a negative study finding clearly demonstrates that DAART resources should not be squandered on patients without known problematic adherence. Future trials of DAART should focus only on patients who are likely to derive benefit.

Acknowledgments

Funding/Support: Dr Altice receives support from the National Institutes on Drug Abuse (grants R01 DA13805, R01 DA017059, and K24 DA 0170720).

References

1. Gross R, Tierney C, Andrade A, et al. AIDS Clinical Trials Group A5073 Study Team. Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naïve HIV-1-infected patients: a randomized trial. *Arch Intern Med* 2009;169(13):1224–1232. [PubMed: 19597072]
2. Altice FL, Friedland GH. The era of adherence to HIV therapy. *Ann Intern Med* 1998;129(6):503–505. [PubMed: 9735090]
3. Wohl AR, Garland WH, Valencia R, et al. A randomized trial of directly administered antiretroviral therapy and adherence case management intervention. *Clin Infect Dis* 2006;42(11):1619–1627. [PubMed: 16652320]
4. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis* 2007;45(6):770–778. [PubMed: 17712763]
5. Macalino GE, Hogan JW, Mitty JA, et al. A randomized clinical trial of community-based directly observed therapy as an adherence intervention for HAART among substance users. *AIDS* 2007;21(11):1473–1477. [PubMed: 17589194]