HIV clinical trials are not enough

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To determine the ultimate benefit of antiretroviral drug regimens for HIV infection, it is essential to begin with treatments whose efficacy has been demonstrated. This is usually done in the highly controlled environment of a clinical trial, which, if properly conducted, will demonstrate internally valid results about the outcome of a given therapy in a group of patients considered eligible for the trial.

In clinical trials of antiretroviral drugs, such as the first clinical trials of zidovudine, clinical outcomes were used as evidence of efficacy.[1] It was later shown that favourable clinical outcomes were associated with viral load reductions.[2,3] The new paradigm of HIV therapy is complete suppression of viral replication to preserve and restore immune function and to delay or prevent the emergence of drug resistance.[4] Hence, drug efficacy is now being measured in clinical trials by the degree and duration of viral load reduction. Clinical trials designed to demonstrate favourable outcomes in terms of reduced morbidity and mortality require prolonged follow-up and large numbers of patients, and they are often not feasible because new therapeutic strategies may be introduced during the study period. This leaves the demonstration of such clinical benefits to other methodologies, including the use of long-term observational databases.

It is necessary to obtain data about the effectiveness of treatments in important groups of patients who may be underrepresented in HIV clinical trials. These groups include women, or at least pregnant women, children, injection drug users, people with language or cultural barriers, and people with comorbidities such as hepatitis C or B, who are typically excluded from trials because of their liver function test results. Observational databases can seek to address the broader range of conditions that exist when a treatment is used in a wider population of subjects with different treatment histories, different levels of adherence and monitoring, and different clinical characteristics. For example, clinical trials of antiretroviral therapies that limit enrolment to patients who have never before received such therapy would not be expected to be reproduced among patients who have received various antiretroviral therapies previously.

In order to move from clinical trials to the determination of treatment effectiveness in the community, a number of issues beyond pure efficacy must be considered: these include provider factors (e.g., which patients will be offered what regimens, how will treatment be monitored, how will adherence be supported and assessed, when and how will regimens be altered); patient factors (e.g., do patients seek and accept treatments, do they adhere to treatments, when and why do they discontinue treatments); and factors related to coverage (e.g., what proportion of HIV-infected people are under medical care and what proportion of these people are being cared for by physicians with expertise in HIV care).

To address some of these issues, which cannot be addressed in HIV clinical trials, a variety of observational databases are being used, including research cohorts (e.g., the cohort used in the Multicentre AIDS Cohort Study[5]), single-centre clinical care cohorts (e.g., the Southern Alberta Clinic cohort[6]), multicentre observational databases (e.g., the HIV Ontario Observational Database,[7] the US Centers for Disease Control and Prevention Adult Spectrum of Disease database[8] and the AIDS Research Consortium of Atlanta Database[9]), and databases set up for the purpose of administering drug treatment programs. An example of the last category is the database for the HIV/AIDS Drug Treatment Program in British Columbia, used by Dr. Robert S. Hogg and associates (page 659),[10] in which demographic and clinical data are augmented voluntarily by patients and physicians.

Each type of observational database has its strengths and weaknesses, and no single database is likely to provide answers to the many important questions in clinical management, quality of care and community effectiveness that are required to best serve the needs of people living with HIV infection. Single-centre studies are likely to have more control than other types of observational databases over the quality of the clinical data available for collection and analysis; however, they also suffer from limitations in

representativeness, because the care is administered by specific providers and may in some instances be provided to a specific patient population. In addition, research databases may be influenced by the Hawthorne effect; that is, the very participation in the research process may alter the behaviour of providers or patients, or both. This effect is much less likely to be seen in databases that extract information on routine care delivered at various sites by a large number of providers, and in administrative databases such as the one used by Hogg and associates.

Hogg and associates have used the strongest type of data for assessing the impact of treatment in the community because the database contained information obtained from a large number of unselected providers and patients who were not influenced by research participation. Such a database can thus help in determining what actually happens in the application of treatment guidelines developed by experts in response to evidence from clinical trials. Hogg and associates have demonstrated significant population-based reductions in the rates of death and progression to AIDS among HIV-infected people treated with ERA-III antiretroviral drug regimens (2 nucleoside analogue reverse transcriptase inhibitors [NRTIs] plus either a protease inhibitor or a non-NRTI) when compared with people given an ERA-II regimen (2 NRTIs), after controlling for important prognostic factors, such as prophylaxis for *Pneumocystis carinii* pneumonia or *Mycobacterium avium* infection, and CD4+ cell count. The clinical benefit of ERA-III therapy was shown despite the authors' use of an intention-to-treat approach, in which people who switched from an ERA-II regimen to an ERA-III regimen were retained in the original ERA-II treatment group for the analysis. This means the effectiveness of ERA-III regimens was likely an underestimate. In addition, Hogg and associates limited their study to people who were receiving antiretroviral therapy for the first time; further analyses are necessary to determine the impact of ERA-III therapy in people with prior antiretroviral drug experience.

The study by Hogg and associates helps to reassure both clinicians and policy-makers that the early treatment benefits of ERA-III therapy suggested in clinical trials can also be achieved in a general HIV-infected population under medical care. Longer follow-up will be needed to determine whether these benefits will last and to monitor adverse effects of treatment. Other, more focused community studies will be needed to evaluate how far this reduction in the rate of progression to AIDS is from the optimal rate that could be achieved and to examine the role of provider and patient factors in determining the current level of community effectiveness. Only then can we seek realistic strategies to achieve the best possible outcomes for Canadians living with HIV infection.

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