One step forward, two steps back

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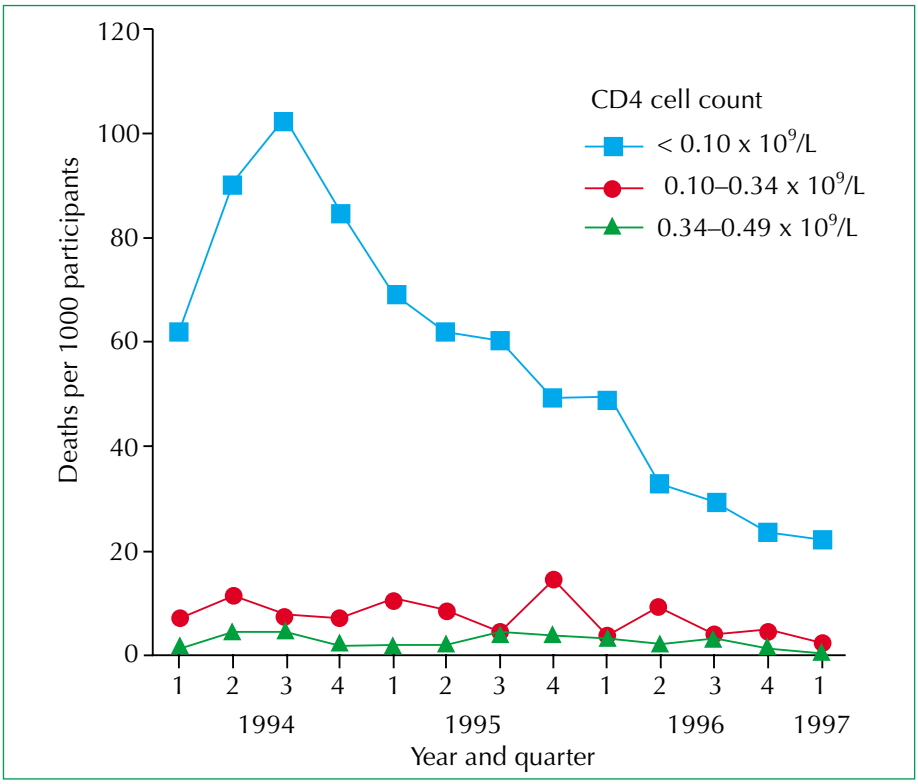
In Canada and beyond, 1997 was a year of gains and losses in the battle against HIV/AIDS. On the one hand, we witnessed significant advances in HIV therapies as well as unprecedented reports of sharply declining death rates attributed to these advances in many developed countries, including Canada[1] (see graph). After 15 years of intensive HIV/AIDS investigation, investments in clinical research finally provided significant dividends in terms of reduced morbidity, improved quality of life and extended survival. Indeed, there were numerous reports in the lay press of people with HIV/AIDS who returned to productive lives after having given themselves up for dead. Sadly, however, these positive developments were overshadowed by new reports of drug resistance, rising incidence rates in key at-risk populations, and the grim reality that potent combinations of HIV therapies remained inaccessible, not only to those in the developing world, but also to certain populations here at home. In this report, we highlight the past year in HIV/AIDS research and describe challenges for the year ahead.

Recent declines in the rate of death from AIDS in many developed countries have been largely attributed to advances in treatment, many of which were reported at the XI International Conference on AIDS, held in Vancouver in 1996. These include double combination therapies (e.g., zidovudine [AZT] and lamivudine [3TC]), which have rendered monotherapy essentially obsolete. Hopes were further buoyed by the advent of protease inhibitors, which led to the development of triple drug combination regimens throughout 1996 and 1997. During 1997 plasma HIV-1 RNA determinations (often referred to as viral load) usurped the CD4 cell count as the most important laboratory marker of HIV disease progression and of therapeutic efficacy.[2] These research findings rapidly converged to have important implications in the clinical setting. For example, clinical decision-making surrounding HIV therapy is now driven by plasma HIV-1 viral load, and the goal of current therapy is to suppress viral replication to below the limits of detection. Reports of undetectable levels of HIV-1 following aggressive treatment in early HIV infection prompted speculation that the virus could actually be eradicated, although others cautioned that reservoirs of HIV-1 in lymphoid tissues



Quarterly death rates among participants receiving antiretroviral therapy through the British Columbia HIV/AIDS Drug Treatment Program, stratified by CD4 cell count. Reprinted, with permission, from Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K, Schechter MT, et al. Decline in deaths from AIDS due to new antiretrovirals [letter]. *Lancet* 1997;349:1294. ©1997 The Lancet Ltd.

can remain impervious to treatment. Nevertheless, in 1997, previous uncertainty regarding the ideal time to start antiretroviral therapy gave way to the new ideology: "Hit early and hit hard."

Yet 2 sombre facts have detracted from this new-found optimism. Drug resistance, which has been the bane of all antiretroviral drugs to date (e.g., AZT, 3TC, didanosine), was also demonstrated for each member in the class of heralded protease inhibitors. Reports of HIV-1 rebound are reminiscent of the first reports of AZT resistance in the late 1980s, a salient reminder that the proverbial cure is not around the corner. Moreover, because 90% of all HIV infections continue to occur in developing countries, the question arises about how to deliver therapies to countries that need them the most. In Canada, it was recently found that 60% of the HIV-infected injection drug users (IDUs) in British Columbia who were eligible to receive antiretroviral therapy through the province-wide HIV/AIDS treatment program had not been prescribed any. In Ontario, a shocking number of HIV-positive infants had been born to untreated HIV-infected mothers, 3 years after it was standard practice to offer antiretroviral prophylaxis to pregnant women. If it is reasonable for us to expect that all HIV-infected people should benefit from advances in HIV treatments, such findings prompt a reality check into how treatments are delivered, and to whom.

Although the US has redoubled its efforts to develop an HIV vaccine by the year 2000, phase III trials for the most promising vaccine candidates have yet to begin. Meanwhile, in 1997 intriguing findings continued to surface regarding mutations in genes that encode the coreceptors for HIV-1 cell entry.[3] Mutations in genes for the CCR5 and CCR2 coreceptors have now been shown to be protective against HIV-1 disease progression, and these mutations appear to be present in 30% to 40% of people in most ethnic groups. In about one-third of long-term survivors who avoid AIDS progression for 16 years or more, the relatively benign course can be explained by a CCR5 or CCR2 mutation.[3] The search is now on for agents that attempt to block these receptors and that may provide critical new avenues for treatment.

One of the greatest challenges continues to be in the realm of HIV prevention, with mounting evidence of rising incidence rates on a number of fronts. Current estimates are that 3000 to 5000 new cases of HIV infection will have occurred in Canada this year, a situation not unlike that in the early to mid 1980s. The numbers of new cases are increasing rapidly among IDUs, aboriginals and women. In Vancouver a catastrophic outbreak of HIV infection among IDUs recently occurred, with estimates of annual incidence rates reaching as high as 18%.[4] As a result, recommendations for harm reduction have been brought forward from a national task force to expand syringe coverage, outreach and drug treatment options, and piloting of medical prescription of narcotics. Similar outbreaks have occurred in such cities as Edinburgh and Bangkok and are now also being seen in parts of eastern Europe. That the Vancouver outbreak occurred suddenly, after many years of relatively stable incidence and prevalence rates of HIV among IDUs, should serve as a warning against complacency for those cities still observing stable patterns in this high-risk group. There is also grave concern regarding unexpectedly high HIV incidence rates and relapse to unsafe sex practices among young gay men, who remain at high risk of HIV infection despite a decade of prevention efforts.

The rising infection rates represent much preventable human suffering.

HIV continues to be a most challenging adversary. Sadly, the rising infection rates represent much preventable human suffering and an inexorable guarantee that HIV will continue to be a significant part of the Canadian landscape for decades to come. This past year, considerable progress was made in the treatment of HIV infection, but much ground was lost in preventing new cases. Regrettably, we took one step forward, two steps back.

References

1. Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K, Schechter MT, et al. Decline in deaths from AIDS due to new antiretrovirals [letter]. *Lancet* 1997;349:1294.
2. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
3. Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, et al. Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. *Science* 1997;277:959-65.
4. Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, et al. Needle exchange is not enough: lessons from the Vancouver Injecting Drug Use Study. *AIDS* 1997;11(8):F59-65.

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