

# AIDS in the World II

Global Dimensions,  
Social Roots,  
and Responses

*The Global AIDS Policy Coalition*

*Edited by*

Jonathan M. Mann *and* Daniel J. M. Tarantola



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## *Long-time Survivors: What Can We Learn from Them?*

ROBERT COLEBUNDERS

As the AIDS pandemic grows older, increasing numbers of long-term survivors have been identified. Scientific interest in HIV-infected individuals who have remained healthy for many years is growing rapidly, for they may help discover characteristics related to survival.

The median time between HIV infection and AIDS is estimated at about 10 years, and median progression from AIDS to death is about 2 years.<sup>1-5</sup> In the industrialized world, the incubation period of AIDS has apparently lengthened, perhaps as a result of better patient care, including prophylactic antiviral and antibiotic treatment.<sup>6,7</sup> In developing countries, however, patients generally die considerably sooner.<sup>8</sup> Progression rates towards AIDS also differ considerably among individuals; some develop AIDS within 2-4 months after infection, while others can and do remain healthy for more than 16 years.<sup>9,10,11</sup>

Seven to 12 years after infection, approximately 10 percent of persons with HIV infection maintain a stable number of CD4 lymphocytes.<sup>12,13</sup> However, even among these "non-progressors," immune system abnormalities have been observed. This suggests that over time, all HIV-infected individuals may eventually develop AIDS.<sup>14</sup> (HIV-2 infection progresses much more slowly towards disease than HIV-1 infection [Chapter 12]).<sup>15</sup>

Thus far, of the relatively few published studies of long-term survivors, most involve homosexual men (Table 11-1).<sup>16-26</sup> In nearly all studies only small numbers of persons were included. Several common virological and immunological characteristics have been observed among long-time survivors: a low infectious virus load; infection with a less cytopathic HIV strain or a genetically defective HIV strain; absences of enhancing antibodies; Th1 cell response > Th2 cell response; a strong CD8 positive cell HIV suppressive activity; strong HIV-specific CTL responses; the absence of p24 antigen and presence of p24 antibodies; and intact lymph-node architecture.<sup>27-38</sup> The interpretation of these findings is difficult, as long-term survivors are a heterogeneous group of people, including slow-progressors and non-progressors. Non-progressors seem to maintain high levels of CD4 lymphocytes and to control viral replication without increased CD8 positive cell activity.<sup>39</sup>

**Table 11-1** Cohort studies of HIV-infected people initiated in the early-to-mid-1980s

Cohort study	Date started	Cohort size at onset of study
Homosexual men		
San Francisco men's health study <sup>1,2</sup>	1984	290
San Francisco city clinic cohort <sup>3</sup>	1978-83	583
Multicenter AIDS cohort study (U.S.) <sup>4,5</sup>	1984-85	2,168
Atlanta cohort <sup>6</sup>	1982-83	75
Vancouver lymphadenopathy AIDS study <sup>4</sup>	1982-84	348
Amsterdam cohort <sup>7,8</sup>	1984-85	273
London cohort <sup>9</sup>	1982-84	173
Stockholm cohort <sup>10</sup>	1982-83	115
Persons with hemophilia		
Edinburgh hemophilic cohort <sup>11</sup>	1984	18
London hemophilic cohort <sup>12,13</sup>	1979-85	111
Italian hemophilic cohort <sup>14</sup>	1981-86	119
Heterosexuals		
Prostitutes, Kigali, Rwanda <sup>15</sup>	1984	29

<sup>1</sup>H. W. Sheppard, W. Lang, M. S. Ascher, et al., "Characterization of non-progressors: Long-term HIV-1 infection with stable CD4+ T-cell levels," *AIDS* 7(1993):1159-1166.

<sup>2</sup>H. W. Jaffe, W. W. Darrow, D. F. Echenberg, et al., "Acquired immunodeficiency syndrome in a cohort of homosexual men," *Annals of Internal Medicine* 103(1985):210-214.

<sup>3</sup>S. Buchbinder, M. Feinberg, B. Walker, P. O. Malley, and M. Katz, "Factors associated with long-term non-progression in HIV-infected men," Abstract 454, presented at the VI International Congress for Infectious Diseases, Prague, Czechoslovakia, April 1994.

<sup>4</sup>M. T. Schecter, K. J. B. Craib, N. L. Thinh, et al., "Progression to AIDS in seroprevalent and seroincident cohorts of homosexual men," *AIDS* 3(1989):347-353.

<sup>5</sup>C. G. Lyketsos, D. R. Hoover, M. Guccione, et al., "Depressive symptoms as predictors of medical outcomes in HIV infection," *Journal of the American Medical Association* 270(1993):2563-2567.

<sup>6</sup>J. E. Kaplan, T. J. Spira, D. B. Fiscbein, et al., "Six-year follow-up of HIV-infected homosexual men with lymphadenopathy," *Journal of the American Medical Association* 260(1988):2694-2697.

<sup>7</sup>I. P. M. Keet, A. Krol, M. Klein, et al., "Characteristics of long-term survival early and late in HIV infection," Abstract WS-C03-3, presented at the IX International Conference on AIDS, Berlin, Germany, June 1993.

<sup>8</sup>M. Koot, I. P. M. Keet, A. H. V. Vos, et al., "Prognostic value of HIV-1 syncytium-inducing phenotype of rate of CD4+ cell depletion and progression to AIDS," *Annals of Internal Medicine* 118(1993):681-688.

<sup>9</sup>G. E. Kelly, B. S. Stanley, and I. V. D. Weller, "Natural history of human immunodeficiency virus infection: A five-year study in a London cohort of homosexual men," *Genitourinary Medicine* 66(1990):238-243.

<sup>10</sup>A. Karlsson, G. Bratt, G. Van Krogh, et al., "Prospective study of 115 initially asymptomatic HIV-infected gay men in Stockholm, Sweden," *Scandinavian Journal of Infectious Diseases* 23(1991):431-441.

<sup>11</sup>R. J. G. Cuthbert, C. A. Ludlam, J. Tucker, et al., "Five year prospective study of HIV infection in the Edinburgh haemophilic cohort," *British Medical Journal* 301(1990):956-961.

<sup>12</sup>C. A. Lee, A. N. Phillips, J. Elford, et al., "Progression of HIV disease in a haemophilic cohort followed for 11 years and the effect of treatment," *British Medical Journal* 303(1991):1093-1096.

<sup>13</sup>A. N. Phillips, C. A. Sabin, J. Elford, et al., "Prospects for long-term AIDS-free survival after HIV infection," Abstract 22, presented at the IV European Conference on Clinical Aspects and Treatment of HIV Infection, Milan, Italy, 1994.

<sup>14</sup>E. Santagostino, A. Gringeri, D. Cultraro, et al., "Slow progression of HIV disease in a cohort of Italian hemophiliacs with normal CD4 cell counts for at least 7 years," Abstract 28, presented at the IV European Conference on Clinical Aspects and Treatment of HIV Infection, Milan, Italy, 1994.

<sup>15</sup>E. Bulterys, E. Nzabihimana, A. Chao, et al., "Long-term survival among HIV-1-infected prostitutes," *AIDS* 7(1993):1269-1285.

Much less is known about long-term survivors' lifestyle and other personal characteristics. While it has been proposed that re-exposure to HIV and other sexually transmitted infections may be a cofactor for disease progression, most studies have not found an association between the practice of safer sex and long-term asymptomatic HIV infection.<sup>40-43</sup> The role of other infections (e.g., cytomegalovirus, herpes, HTLV-1, and mycoplasma) as cofactors for disease progression also remains unclear.<sup>44,45</sup> Cigarette smoking may alter the immune response to HIV-1 infection but appears to have no marked effect on clinical outcome.<sup>46</sup> Finally, in cohorts of persons who acquired HIV infection through injecting drug use, abstaining from drugs was not associated with long-term asymptomatic HIV infection.<sup>47,48</sup>

People with HIV infection often state that long survival is associated with a better psychological response and a positive attitude towards HIV infection.<sup>49</sup> However, this has been very difficult to assess. A positive attitude may also be characteristic of people who are motivated to recognize infectious complications earlier and who comply with treatment, thus increasing survival time. In a small study among homosexual men in San Francisco, symptoms of depression did predict a more rapid decline in CD4 lymphocyte counts.<sup>50</sup> However, this finding was not confirmed in the larger multicenter AIDS cohort study.<sup>51</sup>

Age also influences the rate of progression to AIDS. In general, HIV infection progresses more rapidly in infants, while children with hemophilia develop AIDS more slowly than adults.<sup>52</sup> After childhood, the influence of age on progression rates is less clear. Among men with hemophilia, older men develop AIDS more rapidly than younger men; among homosexual men, however, the opposite is true.<sup>53</sup>

Recently it has been suggested that genetic factors may help explain differences in disease progression, and an association has been declared between certain HLA haplotypes and progression of HIV infection.<sup>54,55</sup>

To identify factors associated with long-time survival, further study of "non-progressors" must be compared with people progressing rapidly to AIDS. Such studies should also include people from developing countries. Thus far, only a few natural history studies have been performed in the developing world, and long-term follow-up was not obtained in any of them.<sup>56</sup> Also, dates of HIV infection are generally not known in developing countries, and HIV diagnosis is often made only when patients are hospitalized in an advanced stage of their disease.

Also, since clinical and immunological non-progression over a period of at least 7 years is exceptional in HIV infection, studies require multicenter collaboration. Cohort studies initiated more than 10 years ago are particularly useful for investigating long-term survival (Table 11-1). Individuals infected with HIV are enthusiastic about participating in such studies. The current absence of good hypotheses to explain the differences in progression rates suggests that it is unlikely that a single factor will be identified to explain long-term survival. A large number of factors are probably involved, and their discovery should be an urgent scientific priority.

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