

tile of energy expenditure in the study by Manson et al. These two studies, one in men and one in women, show either a threshold effect⁸ or a progressive decline with progressive activity,⁴ possibly because of differences in the range of activity in the populations. Approximately half the studies that have been published suggest that vigorous activity is required for a reduction in the risk of coronary heart disease.⁷ In populations in which the reference group is relatively active, vigorous activity may be required in order to show a difference in coronary heart disease events,⁷ although Manson et al. found a benefit with both vigorous activity and walking. The classification of activity is also problematic. Many studies define vigorous activity as that requiring an energy expenditure of more than 6 MET, but less exertion can be vigorous for elderly and unfit persons. The study by Manson et al. defined vigorous activity as that producing sweating or tachycardia, but even these physiological responses depend on the level of fitness.

Despite such methodologic problems, the overwhelming evidence supporting the beneficial effects of physical activity on the risk of coronary heart disease warrants the recommendation by health care professionals of regular exercise for most patients. The Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) recommend at least 30 minutes of moderately intense physical activity on most, and preferably all, days of the week.⁹ Moderately intense exercise is that which results in mild shortness of breath and involves oxygen uptake that is approximately 50 percent of the maximal level; an example of such exercise is brisk walking. This recommendation does not prohibit getting more exercise and was never intended either as a definition of the optimal exercise level or to discourage people from exercising more. The data presented by Manson et al. suggest that an hour per day of moderately intense exercise is closer to optimal, and most evidence suggests that progressive amounts of exercise lead to a progressive reduction in cardiac risk. A meta-analysis of 30 cohort studies involving more than 2 million person-years of observation demonstrates a nearly linear decline in the risk of coronary heart disease with increasing levels of physical activity.¹⁰ The National Runners' Health Study demonstrates progressive increases in high-density lipoprotein cholesterol and reductions in blood pressure and obesity in both men¹¹ and women¹² with increasing exercise levels that are considerably higher than those recommended by the CDC and ACSM.

Consequently, although the CDC-ACSM exercise recommendations are prudent, physicians should, in my opinion, recommend them as a minimal level of daily exertion. A lower level of exertion is also beneficial,⁴ and more vigorous exercise, for those who are

so inclined, is probably more beneficial, but also carries a cardiovascular risk, especially for those who are usually inactive.¹³ People should try to exercise daily to minimize the number of days missed and because many of the effects of physical activity on risk factors such as glucose levels, triglyceride levels, and blood pressure are, in part, acute effects of recent exercise.¹⁴

We, as a society, continue to evolve. Data such as those provided in this issue of the *Journal* suggest that the evolution of healthy lifestyles should include a hefty dose of one of our earliest evolutionary steps — walking and other forms of physical activity.

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HIV-1 SUPERINFECTION — A WORD OF CAUTION

ACUTE human immunodeficiency virus type 1 (HIV-1) infection is typically associated with an influenza-like syndrome, with levels of virus in the

bloodstream during the initial symptomatic period typically in excess of 10 million particles per milliliter.¹ These acute symptoms usually resolve within one to two weeks, and there is a gradual reduction in viremia to a mean of about 30,000 particles per milliliter one year after infection.² This dramatic drop in viremia is thought to be due to the induction of partially effective immune responses against the virus, although without treatment, viremia slowly rises over time. The conclusion that the initial containment of the virus represents a partially protective immune response is supported by studies in animal models of AIDS, in which initially high levels of virus persist when the CD8 subgroup of T lymphocytes is experimentally removed.³ Together, these observations suggest that effective immune responses against HIV-1 are generated, even if they are ultimately incapable of preventing the progression of disease.

Another way to address the effectiveness of immunity induced by HIV-1 infection is to examine whether infection with one HIV-1 strain can provide protection against superinfection with a second strain after partial containment of the first virus. More than a dozen different subtypes of HIV-1, called clades, have been identified around the world, and they can differ from one another by 30 percent in the *env* gene sequence and 15 percent in the *gag* gene sequence. Although numerous cases of simultaneous new infection with two distinct HIV-1 strains have been reported,⁴ there have been few, if any, clear cases of superinfection, in which a second virus infects the host well after a quasi-steady state with the first virus has been achieved. Although experimental models of AIDS in animals indicate that superinfection is possible,⁵ documentation of such a phenomenon in humans has been lacking. The assumption that superinfection does not occur in humans infected with HIV-1 has bolstered hopes that it might be possible to develop a broadly cross-protective AIDS vaccine and probably has also influenced decisions among consenting HIV-1-infected partners about whether to follow safe-sex recommendations.

In this issue of the *Journal*, Jost et al.⁶ challenge these assumptions and provide convincing evidence that HIV-1 superinfection can occur long after an initial infection is established. In the case they describe, primary infection with HIV-1 clade AE, which is prevalent in Southeast Asia, was documented in 1998. For the ensuing 28 months, the only virus detected in the patient was of the same AE clade. During this period, the patient was successfully treated with a four-drug regimen against HIV-1. Then, three months after he stopped treatment because of drug toxicity and three weeks after he had additional sexual contacts in Brazil, B clade HIV-1, which is endemic in Brazil, was detected when he had a sudden rebound in viremia.

Although the B clade-infected person in Brazil who transmitted the virus could not be identified and thus unequivocal evidence of superinfection could not be documented, these data strongly support the conclusion that this patient was first infected with an AE clade virus and was superinfected more than two years later with a B clade virus that accelerated the progression of disease. Similar HIV-1 superinfection with two different clades has also recently been described in two injection-drug users in Thailand.⁷

Where does this leave HIV-1 vaccine initiatives, if it can be demonstrated that anti-HIV-1 immunity cannot provide protection against infection with different clades of the virus? There are aspects of this case that need not leave us in despair. First, the HIV-1-specific immune responses that were detectable were narrowly directed and insubstantial, with cytotoxic T lymphocytes targeting only a single region of the virus identified. The typical gradual broadening of immune responses may have been blunted by early and effective treatment⁸ and may have further waned during the period of effective antiviral therapy. Second, cases of superinfection occurring as a consequence of exposure to a genetically different clade of virus do not define the likelihood of such events. Exposure to a homologous clade of virus is probably far more frequent than exposure to genetically different clades and therefore more relevant to vaccine programs. Thus, if a vaccine can induce, in fully immunocompetent persons, broadly based HIV-1-specific immune responses that are associated with successful control of viremia, the vaccine may be successful even in the face of a rare challenge by a very different clade of virus. Finally, most programs of HIV-1 vaccine development already assume that protection against multiple clades will be difficult to achieve. Indeed, the viral variation in HIV-1 infection far exceeds that observed in influenza,⁹ yet the influenza virus diverges sufficiently over time to require a new vaccine annually. Studies of animal models have already shown that achieving protection against divergent AIDS-causing strains of virus is likely to be a formidable task⁵ and may require the development of polyvalent vaccines.

The less optimistic view of this case is that it may be the tip of the iceberg — that superinfection may be frequent and may explain the presence of recombinant viruses worldwide. The fact that the first descriptions of superinfection in humans involve heterologous clades of virus may simply reflect the fact that it is easier to demonstrate superinfection when two distinct clades are involved than when only one clade is involved. It is worth remembering that only a tiny fraction of CD4 T lymphocytes are infected at any one time, presumably leaving an ample number of uninfected cells available as targets for the superinfecting viral strain. Caution should be exercised in concluding

that the immune response was necessarily weak in the patient described by Jost et al., since only previously defined epitopes of cytotoxic T lymphocytes were tested for recognition and since virus-specific helper T-lymphocyte activity and neutralizing antibody levels were not determined. It is also difficult to ignore the fact that this patient expressed two of the HLA class I molecules most consistently associated with effective control of HIV-1 — namely, HLA-B*57 and HLA-B*51. In the worst-case scenario, superinfection with a virus differing by only one amino acid in a critical epitope might be associated with lack of immune control and progression to AIDS.¹⁰

The public health implications of this and other cases of superinfection are clear. The data show that infection with HIV-1 does not necessarily provide protection against superinfection with another clade of HIV-1, even though they do not reveal how likely it is that such superinfection will occur. Almost by definition, a superinfecting strain of virus will be one that is not well contained by the immune response to the primary strain. Thus, superinfection may precipitate more rapid progression of disease. Infected and non-infected persons should therefore exercise the same degree of vigilance to prevent HIV-1 exposure. With sexual activity seemingly increasing among persons with HIV-1 infection,¹¹ this is a public health message that needs to be broadcast loud and clear.

The current case report leaves a number of questions open, but these questions will clearly help focus future research efforts. For example, to what extent is the increasing number of recombinant viruses worldwide the result of superinfection? Does superinfection occur within clades? Can such cases be used to begin to dissect the components of protective immunity in HIV-1 infection? We urgently need detailed evalua-

tions of the immune responses and of the sequences of circulating virus before and after loss of control of viremia in cases of superinfection. The magnitude of the task of creating an effective AIDS vaccine will then become more apparent.

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