We read with interest the article by Worm and colleagues, who reported no significant association between current or recent protease inhibitor exposure and sudden death or nonhemorrhagic stroke in the D:A:D study [1]. The investigators reported 78 sudden deaths over 234,818 patient-years of follow-up, a rate of 0.33 cases per 1000 patient-years (95% confidence interval [CI], 0.26–0.41).

First, we would like to clarify the issue of PR prolongation. Worm et al. write, “Prolongation of the PR interval could be an early manifestation of an ongoing conduction defect that may lead to complete AV block. Although rarely seen without other cardiac abnormalities, one possible clinical manifestation of severe PR interval prolongation may be congestive heart failure” [1, p535]. Recent observational studies suggesting more heart failure hospitalizations or higher all-cause mortality were in individuals with known coronary artery disease and a PR interval of >220 msec [2] or >200 msec [3], respectively. Thus, PR prolongation of <200 msec alone, in the absence of Mobitz type II second degree block or a widened QRS interval, is of no prognostic significance for progression to advanced AV block [4], heart failure, or mortality. The PR interval is well-known to vary by the time of day the electrocardiogram is taken (a reflection of variation in vagal tone that influences AV nodal conduction), drugs taken (such as beta blockers), and heart rate. PR prolongation may also be a marker of heart failure because often such patients are prescribed beta blockers, which can prolong AV nodal conduction and thus the PR interval.

Second, we found a mean sudden cardiac death rate of 2.6 cases per 1000 person-years (95% CI, 1.8–3.8) over a 10-year period in a single-center, retrospective cohort study of 2860 consecutive patients receiving care in a public human immunodeficiency virus (HIV) specialty clinic in San Francisco, California [5]. Cardiac deaths accounted for 13% of the overall mortality, and 86% of the cardiac deaths occurred suddenly. Although the sudden cardiac death rate was 4-fold lower than the rate of AIDS-related deaths (11.4 cases/1000 patient-years [95% CI, 9.6–13.6]), it was 4.5-fold higher than the contemporaneous citywide (98% HIV negative) adult sudden cardiac death rate in San Francisco [6], adjusted for age, sex, and ethnicity.

The low sudden death rate reported by Worm and colleagues is in apparent conflict with our observed rate, which is much higher. However, this discrepancy is likely due to a major methodological difference, which is their use of a non-standard definition of sudden death that specifically excluded causes due to coronary artery disease [7]. Coronary artery disease is in fact the largest overall contributor to sudden death, contributing to up to 80% of such deaths, according to many epidemiological studies [8]. Since coronary artery disease is a very important risk factor for sudden cardiac death, we specifically included these causes in our definition.

Therefore, the sudden cardiac death rate reported in the D:A:D study may be some 5-fold lower than the actual rate, since only rare ion channelopathy (genetic) and cardiomyopathy causes of sudden cardiac death are captured after exclusion of coronary artery disease causes. In fact, multiplication of the sudden cardiac death rate reported in the D:A:D study (0.33 cases/1000 person-years) by 5 results in a rate more in range with the sudden cardiac death rate observed in our study (1.65 cases/1000 person-years vs 2.6 cases/1000 person-years). This discrepancy also highlights the difficulties with retrospective observational studies of deaths. For example, although we cross-checked multiple records, how many sudden cardiac deaths were not actually cardiac? What is the contribution of unmeasured factors such as drug use or occult overdoses? What is the role of antiretroviral drugs and coadministered drugs, particularly in terms of QT interval prolongation? Thus, while prior studies may have underestimated sudden cardiac death
rates, we may have overestimated it. Future prospective studies, including systematic autopsy evaluation, which is ongoing at our site, will be needed to provide additional insight into the actual causes of death, as well as the mechanisms underlying this disease process.

Notes

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