The difference in the ratio of spliced to unspliced RNA might also be explained by differences in the effectiveness of the cellular immune response. HIV RNA production by an infected cell goes through several phases. In the early phase the viral transcript gets multiply spliced to express the early regulatory genes and there is no export of unspliced RNA from the nucleus. Only in the late phase of viral expression does unspliced RNA get exported to the cytoplasm. The U/S RNA ratio is therefore strongly dependent on the ratio of cells in the early phase, expressing only spliced RNA, versus the cells in the late phase, expressing also unspliced RNA. Faster killing of the cells in the early phase will not change the U/S RNA ratio, because the number of cells in the later phase depends on the number of cells that complete the early expression phase. Thus, if more early phase cells are killed, the amounts of both spliced and unspliced intracellular mRNA will be reduced proportionately. On the other hand, faster killing of the cells in the later expression phase will significantly reduce the amount of unspliced intracellular mRNA. Therefore, faster killing of infected cells in slow-progressors that have better CTL responses will give rise to a relatively low U/S RNA ratio. Slower killing of infected cells in rapid progressors will give, according to this hypothesis, higher U/S RNA ratio. This is consistent with higher U/S RNA ratios observed (1, 3, 5) in rapid progressors, which is associated (1) with weaker cellular immune responses.

This same hypothesis could explain the longitudinally observed (1, 3, 5) increase of the U/S RNA ratios as being related to weakening of the cellular immune response during the period of disease progression (2). The hypothesis suggested here is in line with the one suggested by Wolinsky et al., that differences in the CTL response are the basis for differences in the rate of disease progression in these patients. A quantitative analysis of the hypothesis, using a mathematical model, gave the same results as described above (6).

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