Transmission of zidovudine resistant strains of HIV-1: the first wave

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In an extremely interesting paper in this issue Goudsmit and colleagues [1] investigate the impact that patients who fail therapy had on the transmission of zidovudine (ZDV)-resistant strains of HIV-1 in the Amsterdam Cohort Study (ACS) from 1990 to 1998. The authors present both new empirical data and analyze a mathematical model in order to explain their empirical findings. Goudsmit and colleagues [1] identified three individuals with ZDV-resistant primary infections by analyzing sequence data from the reverse transcriptase and protease genes of viruses from gay men newly infected with HIV-1. They then used a simple mathematical model to calculate the number of cases of ZDV resistance that were expected to have occurred in the ACS as the result of transmission over this time period. The model was based upon three difference equations, and included three clinical groups: patients infected with wild-type ZDV-sensitive viruses (S), patients infected with ZDV-resistant viruses as a result of suboptimal treatment (R), and patients infected with ZDV-resistant viruses as a result of transmission (I). The parameters in the model varied with time, and were estimated from the ACS data. The model predictions were then compared with their empirical findings.

During the study period the usage level of ZDV monotherapy in the ACS (as in other geographic locations) initially rose and then fell. The first HIV-infected ACS patient was treated with ZDV in 1987, ZDV monotherapy reached a maximum coverage level of 28% during the period 1990–1992, but by the end of 1998 only one ACS patient remained on ZDV monotherapy. As the usage of ZDV monotherapy declined, usage of therapies with protease inhibitors in the ACS increased from 4% to 64% over the period 1994–1998. During the period of study (1990–1998) 43 individuals were identified with a primary HIV-infection; however only three primary infections were determined to be due to the transmission of ZDV-resistant viruses. Sequence analysis determined that one of these patients was infected in 1995, and that the two other patients were infected in 1996. The model, in conjunction with data from the ACS, was then used to predict the expected temporal trends in the prevalence and the transmission of ZDV-resistant strains. Predictions were in agreement with the empirical data and showed that both the prevalence and the transmission of ZDV-resistant strains should have initially increased and then decreased. The prevalence of ZDV resistance in the ACS initially rose (up to a maximum of 22%) due to the large number of patients receiving ZDV monotherapy, and then rapidly decreased after 1996 because patients were switched to more effective therapies. The model predicted that only a few (n = 3) cases of ZDV resistance would have arisen in the ACS due to transmission of ZDV-resistant strains; transmission of ZDV-resistant viruses stopped as the prevalence of ZDV resistance decreased to zero. The authors concluded that the prevalence of ZDV resistance in the ACS was determined mainly by the number of patients on insufficient or failing therapy (i.e., monotherapy with ZDV) and was influenced only slightly by transmission of ZDV-resistant strains.
Epidemics of drug-resistant pathogens have very different dynamics than epidemics of drug-sensitive pathogens. Epidemics generated by drug-sensitive pathogens rise and fall as transmission increases and then decreases; hence transmission drives prevalence. However, epidemics generated by drug-resistant pathogens are not driven by transmission alone, but by a combination of two processes (acquired drug resistance and primary drug resistance). Mathematical models have been used to quantify the relative contribution of these two processes both in initiating and maintaining epidemics of drug-resistant pathogens [2–6]. Initially, the prevalence of drug-resistance is driven by the direct conversion of drug-sensitive cases into drug-resistant cases due to therapeutic failure; this process is known as acquired drug resistance and depends upon both the number of cases receiving treatment and the treatment failure rate. Subsequently, primary drug resistance (i.e., the transmission of drug-resistant strains) can contribute to the prevalence of drug resistance. The usage rate and the treatment failure rate for cases receiving ZDV monotherapy in the ACS were high: therefore the prevalence of ZDV resistance rose to a fairly substantial level resulting from acquired resistance, but then fell as the usage rate of monotherapy declined. The ZDV-resistant strains that evolved were not very fit, therefore the transmission of ZDV-resistant strains remained low (i.e., primary drug resistance was unimportant) and hence the prevalence of ZDV resistance in the ACS declined to zero.

The emergence of drug resistance potentially limits substantially the available therapeutic treatment options for many HIV-infected individuals. Thus it is necessary to understand both the past of the epidemic (in terms of drug resistance), as well as to predict the future of the epidemic of drug resistance. This elegant analysis by Goudsmit and colleagues [1] provides considerable insight into what produced the rise and the fall of ZDV resistance. Their study is in agreement with previous theoretical studies [4,5,6] that have shown that a high usage of failing therapies will lead to a high prevalence of drug resistant HIV-1. It is also possible to predict what is to be expected in the future for other strains of drug-resistant HIV-1 based upon theory, and on this current study. We can expect a series of waves of drug-resistant strains of HIV-1 to move through the treated HIV-infected population. Each new wave will arise as a result of acquired drug resistance due to failure of specific treatment regimens. However, whether each subsequent wave of drug resistance will fall (as occurred with ZDV resistance) or will be maintained by the transmission of the drug-resistant strains will depend upon the replication fitness of the specific strains that evolve. Analyses of other empirical data sets should show time-delayed waves of transmission of drug-resistant strains of HIV-1 rising and falling as specific treatment regimens have replaced each other. If drug-resistant HIV-1 strains evolve (or have already evolved) that have equal or even greater fitness than drug-sensitive strains of HIV-1 their transmission potential will be substantially greater than ZDV-resistant strains. The evolution of such resistant viruses could potentially pose a major clinical and public health problem. ZDV-resistance is only the first wave.

References