Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven

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The clinical goals of HIV treatment are optimally accomplished through consistent high-level adherence to highly active antiretroviral therapy (HAART) and durable suppression of the viral load. However, as a result of the need for lifelong therapy and HIV’s prodigious replication rate and error-prone reverse transcriptase, varying amounts of antiretroviral drug resistance are common in treated individuals. Medication adherence is linked to the development of drug resistance, although not by a simple linear relationship. Recent studies have suggested that extensive drug resistance is not a major determinant of HIV disease progression and death. Rather, failure to access care and discontinuation of or non-adherence with therapy are arguably the most important factors associated with HIV disease progression in the HAART era. Other data indicate that continued therapy in the setting of extensive drug resistance and the inability to achieve viral suppression can provide continued clinical benefit. Such benefit may be mediated, at least partially, by reductions in viral fitness associated with drug resistance mutations.

Keywords: HAART, highly active antiretroviral therapy, treatment

HIV treatment goals and the vicious cycle of failure

The dissemination of highly active antiretroviral therapy (HAART) in wealthy countries has transformed the character of HIV infection from death sentence to chronic disease. The goals of HAART are to maximize life expectancy while maintaining quality of life and minimizing drug toxicity. Because cure is not possible with currently available agents, lifelong therapy is required, a treatment paradigm that is atypical in infectious disease. Appropriately, paramount attention has been directed to achieving and maintaining suppression of the viral load below 50 copies/mL with HAART. Suppression below this level predicts durability of response, maximizes immunological restoration, and, importantly, appears to obviate the evolution of drug-resistant virus. Achieving durable viral suppression requires exceptional medication adherence, and adherence is arguably the most important determinant of survival in HIV-infected individuals in the HAART era.

The need for chronic therapy, coupled with HIV’s prodigious replication rate and error-prone reverse transcriptase, is the engine for drug resistance. Antiretroviral resistance can be detected in a majority of in-treatment HIV-infected individuals in the USA, and is being seen with increasing frequency in newly infected individuals. Failure to maintain viral suppression with antiretroviral therapy instigates a vicious cycle: drug resistance emerges, increasingly complex treatment regimens are required, regimen complexity frustrates adherence, and more drug resistance emerges.

Adherence and HIV drug resistance

The development of drug resistance requires the concurrence of two inherently antagonistic factors: antiretroviral drug exposure and ongoing viral replication. The genetic barrier for resistance varies from drug to drug. Clinically significant resistance to some drugs, notably non-nucleoside reverse transcriptase inhibitors (NNRTIs), can emerge after just a brief exposure to the drug if not combined with other agents. A single point mutation is sufficient to cause high-level NNRTI resistance, and is tantamount to an Achilles’ heel for this class of drugs. Twenty percent of HIV-infected women treated with single-dose nevirapine to prevent perinatal transmission were found to have developed resistance to this agent during follow-up. Moreover, single-dose exposure during pregnancy has been found to be associated with a reduced virological response to nevirapine-based triple drug therapy, used after the pregnancy.

Conversely, clinically-significant resistance to protease inhibitors (PIs) or to nucleoside reverse transcriptase inhibitors (NRTIs) (with the exception of lamivudine) requires the selection of multiple resistance mutations, and more time to evolve. Friedland & Williams suggested that the relationship between adherence and the development of resistance to these drugs may

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be ‘bell-shaped’, in which both high and low levels of adherence pose a relatively low risk of spawning drug resistance. In the case of very high adherence, resistance is stifled by the complete suppression of viral replication. On the other hand, very poor medication adherence fails to provide sufficient drug exposure and selection pressure to compel the evolution of drug resistance. In contrast, intermediate levels of adherence offer ongoing exposure to drug, but also permit low-level or intermittent viral replication and, consequently, pose the highest risk for developing drug resistance.

Data from recent studies have supported this hypothesis. In a group of patients who remained viraemic despite continued use of HAART, Bangsberg and colleagues found that higher levels of objectively-measured adherence were significantly associated with the emergence of PI-associated resistance mutations. Similar findings have been reported from cross-sectional studies. Sethi and coworkers followed self-reported adherence prospectively in a cohort of patients that had achieved HIV RNA < 500 copies/mL on HAART. The highest risk of virological failure and development of new drug resistance occurred in the 70–90% adherence range, with lower risks of new resistance at both higher and lower adherence levels.

**HIV drug resistance and disease progression or death**

Genotypic or phenotypic HIV resistance tests are widely used in clinical practice to inform drug selection in antiretroviral-experienced individuals. Extensive drug resistance can preclude the possibility of viral suppression with available therapy. In the case of tuberculosis, an infection in which treatment issues are analogous to those posed by HIV, multidrug resistance is associated with a markedly increased mortality. However, there are few data addressing the relationship between HIV drug resistance and subsequent clinical disease progression and death.

Recently, our group assessed the implications of antiretroviral drug resistance for HIV disease progression or death in a cohort of 572 HAART-exposed individuals in Baltimore who had genotypic antiretroviral resistance testing carried out as part of clinical care. We hypothesized that greater amounts of drug resistance would be associated with more rapid clinical disease progression because of reduced ability to achieve viral suppression. Patients were categorized ordinarily according to the number of resistance-conferring mutations detected by resistance testing. A higher number of mutations was strongly associated with a reduced likelihood of achieving viral suppression in the 6 months following resistance testing. However, the CD4 cell trajectories were similar in the resistance groups and there were no differences in the occurrence of new opportunistic conditions or death over a median follow-up of 15 months. Compared with patients with 0 to 2 resistance mutations, the adjusted hazard ratio of disease progression or death was 0.9 [95% confidence interval (CI) 0.6–1.4] in those with 3 to 6 mutations, and 0.9 (95% CI 0.6–1.6) in those with ≥ 7 resistance mutations.

Similarly, a group from British Columbia recently published a nested case–control study which found scant evidence that drug resistance was a major factor in HIV-related mortality in the HAART era. In the study, antiretroviral resistance was assessed from the most recently stored plasma samples in 379 HIV-infected individuals who had been exposed to HAART and who died of non-accidental causes between 1997 and 2001. Controls were 1220 living patients who experienced virological failure on therapy during the same calendar period and had resistance testing carried out. Resistance mutations associated with ≥ 2 drug classes were detected in 42% of the living controls, but in just 23% of patients who had died (P < 0.001). Moreover, there was no indication that the prevalence of drug resistance had increased between 1997 and 2001 in the HIV-infected individuals who had died.

The data above were obtained during a period of rapid change in the treatment of HIV-infected individuals, including the introduction of a large number of drugs and growing expertise among clinicians, and therefore cannot be extrapolated to the future. However, an argument can be made that HIV-infected individuals who are entering care currently will be less likely to acquire as much drug resistance (or least to acquire it as rapidly) as those treated in the 1990s because of the exclusive use of combination drug therapy. Many HIV-infected individuals who were in care throughout the 1990s were sequentially exposed to NRTI monotherapy, dual therapy, and finally to PI and NNRTI—essentially a boot camp for HIV drug resistance.

While the findings of the above studies should be tempered by inherent limitations in observational cohort data, the results indicate that antiretroviral drug resistance is not a major determinant of clinical disease progression, at least over moderate-term follow-up. Instead, the public health message that emerges loud and clear, is that underuse of therapy (or non-adherence) remains the major cause of clinical disease progression. In the Baltimore study, the strongest predictor of disease progression following resistance testing was whether or not the patient remained on HAART. Among patients with a CD4 count < 200 cells/mm³ at the time of resistance testing, the risk of subsequent disease progression was five-fold higher in those who discontinued HAART compared with those who continued, whereas the amount of drug resistance was inconsequential. In the British Columbia study, 28% of HIV-infected individuals who had died of non-accidental causes in the HAART era had never used antiretroviral therapy or had < 2 months of exposure, and the amount of drug resistance in the remainder was generally minor.

**Viral ‘fitness’**

Soon after the introduction of HAART, it was observed that patients with highly drug-resistant HIV often maintained stable or increasing CD4 cell counts on therapy, despite persistent virological failure. The term ‘viral fitness’ refers to the ability of virus to replicate in a given environment, and may partially explain the lack of an association between antiretroviral drug resistance and clinical disease progression. Specifically, the mutations that arise with drug exposure allow HIV to continue replicating when drug is present, but only at a cost to the virus. A conceptually straightforward, although partial, measure of relative viral fitness is the replication capacity. In this assay, patient-derived samples of the reverse transcriptase and protease genes are inserted into a standard strain of HIV using a vector that also contains the gene for an indicator protein, luciferase. The replicative capacity of a clinical HIV isolate is defined as the ratio of in vitro single-cycle replication efficiency (quantified by luciferase activity) in the patient-derived construct divided by
that of wild-type strain. Higher and lower replication efficiencies, relative to the standard strain, are indicated by ratios above or below 1, respectively. Replicative capacity has been found to be independently associated with HIV disease progression after adjustment for viral load and CD4 cell count.23

In a revealing study of 16 heavily antiretroviral-resistant patients who discontinued HAART in the setting of persistent virological failure, Deeks and colleagues found that reversion of resistant virus to wild-type virus following a treatment interruption was temporally associated with declines in CD4 cell counts, increases in HIV-1 RNA levels, and increases in viral replicative capacity.24

Conclusions

The clinical goals of HIV treatment are optimally accomplished through consistent high-level adherence to HAART and durable suppression of the viral load. Individuals who fail to access care or who discontinue HAART have the greatest risk of disease progression and death,25 and constitute our highest public health priority. Individuals who fall between these extremes (and most probably do) obtain considerable clinical benefit from HAART, but also may have the highest risk of acquiring drug resistance over time. The identification and development of antiretroviral drug combinations that have a high pharmacokinetic or genetic barrier to resistance are important in the long-term management of HIV. For example, regimens based on a ritonavir-boosted PI appear to be remarkably resistance ‘resistant’.26,27 Innovative and effective adherence interventions are critical in optimizing individual responses to HAART and in minimizing the propagation of drug resistance, and rigorous studies of such interventions are needed.28

It is advisable to continue HAART in individuals with drug-resistant HIV, particularly when the CD4 cell count is <200 cells/mm³, as data strongly suggest that clinical benefits continue to be realized when viral suppression is not achieved. In such situations, the treatment goals include maintaining the individual’s health, avoiding drug toxicity and drug interactions common with complex multi-drug salvage therapy, and preserving potentially active drugs for combination with new agents that become available in the future. For example, it has been suggested that the K103N mutation in reverse transcriptase, which mediates high-level resistance to available NNRTIs, has little detrimental effect on viral fitness.29 Thus, continuing an NNRTI in salvage treatment when K103N is known to exist may provide little clinical benefit, may complicate the use of PI because of drug interactions with the NNRTI, and may select for additional NNRTI mutations that have the potential to quash the activity of second-line NNRTI in the developmental pipeline. In contrast, lamivudine and emtricitabine select for the M184V mutation in reverse transcriptase, which appears to be associated with reduced replicative capacity and to be an evolutionary dead end for the virus. Unlike the situation with other NRTIs or with PIs, where secondary (compensatory) mutations emerge following primary drug resistance mutations to restore the replicative capacity of the virus, no compensatory mutations follow the emergence of M184V. From a clinical perspective, monitoring HIV replicative capacity in individuals with extensive drug resistance may be helpful in selecting the most parsimonious drug combination that maximizes clinical benefit and does not unnecessarily jeopardize future options. However, randomized controlled trials using the replicative capacity assay in this way are needed before such a strategy can be endorsed.

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