EDITORIALS

HIV Integrase Inhibitors — Out of the Pipeline and into the Clinic

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Human immunodeficiency virus (HIV) infection has been transformed over the past two decades from a fatal to a chronic disease, because of combination antiretroviral therapy — a medical triumph.[1] However, HIV has proven to be a masterful escape artist with regard to the pharmacologic agents strategically deployed to block its replication, and the counterpoint to the antiretroviral success story is one of drug resistance and toxicity. For a sizable number of patients who have developed or acquired highly drug-resistant HIV, suffering the ill effects of HIV disease is either a reality or a looming threat.

In most patients with highly drug-resistant HIV, the resistance develops because of sequential exposure to HIV drugs in the context of incomplete virologic suppression. The HIV regimens currently in use are designed to be sufficiently potent to suppress the virus and thus the emergence of drug-resistant mutants. When the adherence to medication is suboptimal or drug absorption or metabolism is altered, viral replication crosses the threshold necessary for the selection and outgrowth of drug-resistant mutants. Unfortunately, the genetic barrier to drug resistance for several of the most important HIV agents is low, requiring only a single point mutation to confer loss of activity. Drug-resistant virus can also be transmitted from person to person and from mother to child, although the transmission of strains resistant to multiple classes of drugs is rare, to date.[2]

For over a decade, we have approached the treatment of drug-resistant HIV as a Sisyphean task, using a strategy that we knew from the start was doomed to fail — the addition of a single new agent to an ailing regimen. This approach was based not on ignorance but on the lack of new classes of antiretroviral agents. The situation is complicated further by our incomplete understanding of cross-resistance and our incomplete ability to predict residual antiretroviral activity associated with the individual agents in the drug classes targeting HIV nucleoside reverse-transcriptase inhibitors and protease inhibitors.

For patients infected with drug-resistant HIV, adding a single new drug to a failing regimen provides temporary benefit yet inevitably leads to the selection of a virus that is even more drug resistant. Some strains that are highly drug resistant replicate less efficiently in vitro than others, but ongoing replication of these strains in vivo is still associated with a decline in immune function. Thus, delaying a switch in regimen places the patient at jeopardy for serious infections and cancers as well as for a circulating strain of HIV more resistant to a future antiretroviral "backbone" regimen. These circumstances back providers and patients into a corner, forcing them to gamble on either a wait-and-see strategy or a switch strategy.

Until recently, the pace of HIV-drug development was not conducive to an aggressive approach to treating patients with a highly drug-resistant virus. Since 2003, nine new drugs and three new drug classes, including HIV integrase inhibitors, were approved for HIV treatment. HIV integrase was a natural target for HIV chemotherapy because of both its central role in the HIV life cycle and the absence of a human homologue. The development of this class of drugs exploited and shed light on the complex multistep process of integration of the HIV provirus into the host genome.[3] Raltegravir, the first compound of this class to be approved for clinical

use, inhibits strand transfer, the third and final step of the provirus integration.

In this issue of the *Journal,* Steigbigel et al.[4] report the findings of the BENCHMRK-1 and BENCHMRK-2 studies (the Blocking Integrase in Treatment Experienced Patients with a Novel Compound against HIV, Merck studies; ClinicalTrials.gov numbers, NCT00293267 and NCT00293254), which evaluated the activity of raltegravir among 699 patients infected with HIV. Only patients infected with HIV that had documented resistance to three classes of HIV drugs were eligible for these studies. The patients were randomly assigned to receive an optimized antiretroviral regimen either alone or in conjunction with raltegravir. The antiretroviral regimens were individually designed on the basis of previous antiretroviral history and results of drug-resistance testing. The regimens were permitted to include darunavir, an HIV protease inhibitor that was not yet licensed at the time of the study.

Patients who received raltegravir had higher rates of virologic suppression than those who received placebo, and the overall rates of viral suppression are among the highest reported for patients infected with HIV with triple-class resistance. Increases in the CD4 cell count were more pronounced in the raltegravir group than in the placebo group; the overall adverse-event profile did not differ between the two groups. Rates of cancer were higher in the raltegravir group. However, the rates of adverse events were low, and differences in the rates from the combined BENCHMRK studies and from a larger data set including other studies of raltegravir were not significant. One could speculate that the earlier occurrence of clinical events in the raltegravir group reflects a more robust immunologic response and unmasking of underlying conditions. Continued monitoring for these and other adverse events in patients receiving raltegravir will be important during its expanded use.

The companion article by Cooper et al.[5] in this issue of the *Journal* underscores the importance of fully active multidrug therapy in sustaining virologic suppression in patients infected with HIV that has multiclass drug resistance. Virologic response rates were 51%, 61%, and 71% when raltegravir was provided in combination with no, one, or two other active drugs, respectively. Data on the high end of this dose–response curve could potentially be even greater when patients are candidates for the CCR5 inhibitor maraviroc, an agent newly approved by the Food and Drug Administration in a new class of HIV drugs expected to have activity against the HIV infecting this population. The 51% response rates on the low end should not encourage the sole addition of raltegravir to the regimen of a patient with multiclass-resistant HIV, which could lead to rapid development of drug resistance. Resistance to raltegravir requires only a single point mutation, and among 94 subjects in the raltegravir group with virologic failure who underwent genotyping, approximately two thirds showed at least one of the known resistance mutations to raltegravir by week 48. As expected, the prevalence of resistance mutations was lower among isolates from patients who were given (in addition to raltegravir) two or more active drugs (33%), as compared with none (78%).

What do these results mean for clinical practice? The results of the BENCHMRK studies usher in a new era for HIV therapy — the expectation that combination regimens involving new agents can suppress even the most drug-resistant HIV. Current HIV guidelines endorse this approach, and clinicians are eager to put it into practice.[6]

At present, raltegravir and other new classes of HIV drugs will be used principally for patients in whom available antiretroviral agents have failed to achieve HIV suppression. It is crucial that new HIV agents are used wisely to maximize benefit and minimize resistance. It is also important to rethink our current HIV treatment strategies and to extend research on these new agents in other populations, such as patients infected with HIV who have never been treated. Given the unmet treatment needs in the global HIV epidemic, it is further incumbent on researchers, policymakers, and advocacy groups to evaluate the optimal use of new agents in low- and middle-income populations and to work toward making the drugs available for both children and adults.

Raltegravir is a powerful weapon for patients combating drug-resistant HIV. However, the low genetic barrier to drug resistance against raltegravir represents a major point of vulnerability.[7] With attention to adherence and with the use of accompanying active antiretroviral agents, the risk can be minimized. Nonetheless, we must acknowledge that even though regimens are sufficiently potent to treat drug-resistant HIV, they

may require a substantial pill burden and use of the injectable drug enfuvirtide. These regimens can be overwhelming even for the most motivated patient. The fact that integrase inhibitors are emerging out of the pipeline and into the clinic shows that persistence and investment in new agents can shed light on basic science, open new doors for research, and most importantly, transform approaches to HIV treatment.

No potential conflict of interest relevant to this article was reported.

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1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
2. Transmission of drug-resistant HIV-1 in Europe remains limited to single classes. AIDS 2008;22:625-35.
3. Hazuda DJ, Felock P, Witmer M, et al. Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. Science 2000;287:646-50.
4. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med 2008;359:339-54.
5. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. N Engl J Med 2008;359:355-65.
6. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society–USA panel. JAMA 2006;296:827-43.
7. Malet I, Delelis O, Valantin MA, et al. Mutations associated with failure of raltegravir treatment affect integrase sensitivity to the inhibitor in vitro. Antimicrob Agents Chemother 2008;52:1351-8.

Noninvasive Monitoring of Tumors

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The treatment of non–small-cell lung cancer has made limited but clinically significant progress during the past two decades of clinical research. Through carefully designed clinical trials, investigators have identified several chemotherapeutic drugs to combat this disease. Many questions have been asked and answered. Which combinations work best? How frequently should they be given and for how long? And which patients should be treated?[1] Nonetheless, such advances have been limited, and the prognosis for patients with advanced disease remains grim.

Despite the modest results achieved with conventional cytotoxic chemotherapeutic agents, the past several decades of basic cancer research have started to yield therapeutic results based on our understanding of cancer biology. The identification of "druggable targets" has emerged from studies dissecting the mechanisms of tumor growth, invasion, and metastases; the evasion of apoptosis; self-sufficiency in growth signaling; insensitivity to antigrowth signals; sustained angiogenesis; and limitless replicative potential — the classic hallmarks of cancer.[2] Some therapies that target these pathways, such as agents inhibiting angiogenesis and cell-signaling pathways, are approved and in the clinic.

An example of how an understanding of basic cancer biology has translated into the clinic is that of the pathway of the epidermal growth factor receptor (EGFR), one of the four members of the HER2/ErbB family of receptors. Ligands bind to the receptor, inducing receptor dimerization and subsequent phosphorylation of intracellular tyrosine kinase–binding sites, leading to the activation of a cascade of downstream signaling events. Activation of these pathways leads to increased cellular proliferation, motility, adhesion, invasion, angiogenesis, and inhibition of apoptosis.[3] Agents have been developed that inhibit this pathway by binding to the extracellular domain of the receptor, as in the case of monoclonal antibodies such as cetuximab and panitumumab, or by binding to the intracellular tyrosine kinase domain, such as erlotinib, gefitinib, and lapatinib.

However, these drugs do not work in everyone. Even though patients whose tumors have an activating mutation in the tyrosine kinase domain are likely to have a high rate of response to EGFR tyrosine kinase inhibitors and prolonged survival,[4] these patients are in the minority. (Approximately 10% of patients in Europe and North America carry activating mutations.) Moreover, the emergence of secondary *EGFR* mutations that inhibit the binding of tyrosine kinase inhibitors has been observed in patients in whom resistance to such drugs has developed.[5] Thus, the