

All HIV Is Not Created Equal: Drug Resistance, Viral Fitness, and Virulence

The Gladstone Connection

The Dream of a World without AIDS

The International AIDS Conference in 1996 was an optimistic high point for HIV researchers and people with AIDS. Combination cocktails of drugs, including protease inhibitors, had recently been found to prolong the lives of HIV-infected persons. The drugs were capable of reducing the amount of virus to levels that were undetectable with routine laboratory tests. Some imagined that the virus that could not be detected might eventually disappear entirely, leading to “viral eradication”—a virologist’s term for “cure.”

The challenges of HIV research quickly reasserted themselves. Important reservoirs of viral infection persist despite our best therapies. Further, virological drug failure, or rebound of viral load in the blood, is common among those starting combination antiviral therapies. The emergence of drug resistance—a major cause of rebounding viral load—is testimony to the vast evolutionary potential of HIV-1. The virus either changes so that drugs are no longer effective or finds ways to exclude the drugs from the life-cycle machinery. In this way, HIV-1 adapts to therapies even as it evades immune responses.

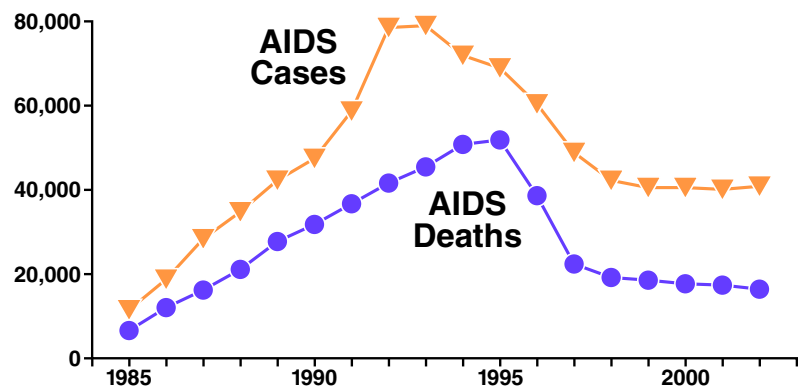
Research at the Gladstone Institute of Virology and Immunology focuses on HIV and the AIDS epidemic. The laboratory of Robert M. Grant studies how clinical health can be preserved despite the appearance of drug-resistant infections. Through collaborative research involving government, private, and academic partnerships, his group also plays a pivotal role in evaluating new drug candidates and therapeutic strategies.

Drug Resistance Sends a Wake-Up Call

Drug-resistant strains of HIV-1 originate in patients receiving antiviral therapy and can be spread to uninfected persons through transmission. These mutated forms of the virus can impair virological responses even in persons who have never taken antiviral drugs. Indeed, in 1997, just 1 year after cocktail combinations came into widespread use, San Francisco was one of the first cities to report the transmission of multidrug-resistant HIV-1. By 1998, the prospect that drug resistance could overwhelm our best therapies was the pessimistic counterpoint to the optimism that prevailed only 2 years earlier.

A clinical observation offered a lifeboat in the rising sea of drug resistance. Although drug-resistant infections were becoming very common in clinical practice, leading to rebounds in viral load during therapy, the clinical illnesses characterized by AIDS remained uncommon in treated patients. Hospital wards devoted to AIDS treatment that had filled to overflowing in the 1980s became quieter after the advent of drug cocktails in 1996. Surprisingly, they remained quiet despite the resurgence of HIV-1 in drug-resistant forms. These patterns suggested that drug-resistant HIV-1 was less virulent and thus less able to cause disease.

Adults and Adolescents with AIDS in the U.S.



The introduction of new anti-HIV therapies in 1995 dramatically changed the course of AIDS in the United States.



A trial led by Dr. Grant's laboratory will determine if a well-tolerated and inexpensive antiviral drug can block the relentless spread of new HIV infections among men, such as these men standing under a health center in Peru. (The center is built above ground because of seasonal flooding of the Amazon River.) Dr. Grant's laboratory is also collaborating with Peruvian investigators and government to establish surveillance for drug-resistant HIV in Peru. The last round of surveillance involved six cities in Peru with a low prevalence of resistance. The data have been presented in international meetings by Dr. Javier Lama of the Peru-based Asociación Civil Impacta Salud y Educación.

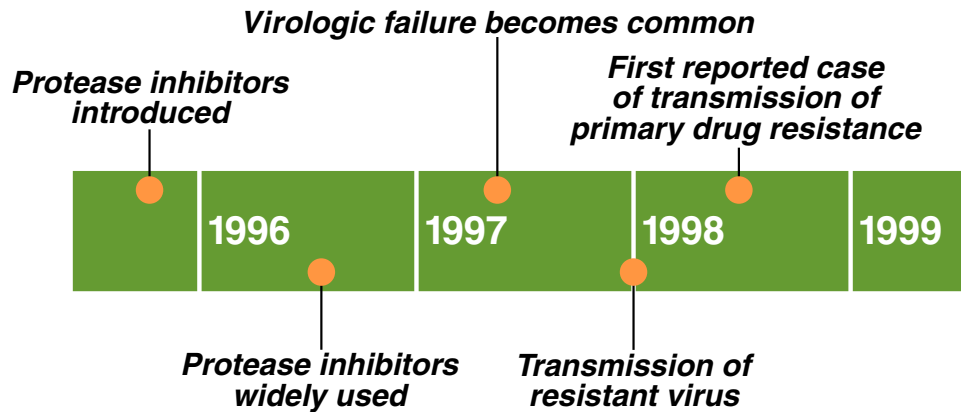


Viral Virulence

Careful observations by investigators in Dr. Grant's group in collaboration with their colleagues at San Francisco General Hospital led to the discovery that patients with drug-resistant infections frequently had preserved immune systems, as indicated by persistently higher CD4 T-cell counts in the blood. The extent of this sparing of the immune system could be linked to persistent decreases in the amount of virus in the blood and other tissues.

Clinical observations suggested that drug-resistant virus does not replicate well. Indeed, laboratory studies performed at Gladstone and nearby biotechnology companies confirmed that drug-resistant HIV-1 had reduced capacity for repli-

Primary Protease Inhibitor Resistance Appears on Time



In a scenario much like that of bacteria and antibiotics, drug-resistant viral strains appeared shortly after the introduction of protease inhibitors.

ation and impaired fitness in the absence of therapy. In most viruses resistant to multiple drugs, the capacity for replication was reduced by more than 75%. Clearly, HIV-1 pays a substantial cost as it adapts to drug therapy. Findings from persons recently infected with drug-resistant HIV-1 confirmed that CD4 counts were often relatively preserved, highlighting the immune-sparing effect of impairments in replication capacity.

Digging deeper into the interplay between virus and cell, Gladstone investigators discovered that drug-resistant HIV-1 was particularly hampered in its ability to infect human thymic tissue. The thymus, an organ lying under the breastbone, “educates” maturing T cells that populate the immune system. Previously, Gladstone investigators found that the thymus increases in size in early HIV-1 infection, in an apparent struggle to cope with the devastating effects of the virus, only to collapse in late-stage infection just before the appearance of end-stage AIDS. The finding that drug-resistant HIV-1 replicates poorly in thymic tissue and spares thymic cells helps explain why people can stay AIDS-free after the appearance of drug resistance. More work is under way to understand the molecular interactions that underlie this cellular preservation.

Insights from Natural Infections

This was not the first time Gladstone investigators observed a disconnect between viral replication and viral disease. Sooty mangabeys, an Old World monkey that is a natural host of the HIV-like simian immunodeficiency virus, never develop AIDS, despite lifelong infection, extremely high viral loads, and relatively weak antiviral immune responses. These seminal findings indicate that immune tolerance may be associated with reduced injury from viral replication.

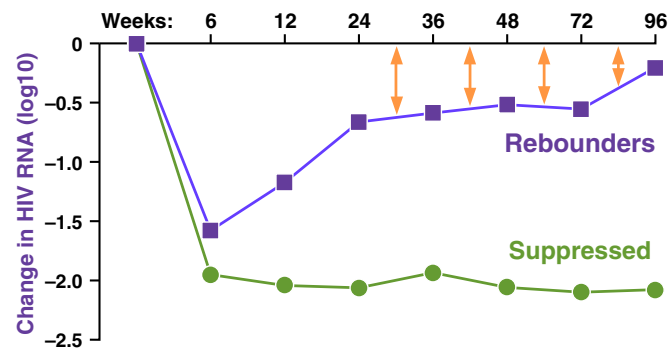
Indeed, drug-resistant HIV infections in humans have several features in common with natural infections of Old World monkeys. The viral load in the blood can be substantial but is not always linked to disease progression. In both settings, there is a relatively quiescent immunological state—a sort of cease-fire. Further research will allow us to learn how this state is maintained, which may translate into immunological interventions for regulating immune responses to be more effective and to avoid injury to bystander cells.

Bench to Bedside

The finding of durable impairments of viral replication in drug-resistant HIV-1 has broad clinical and policy implications. The primary goal of antiviral therapy is still to suppress viral load to very low levels and to prevent drug resistance. Essential for this effort are new classes of drugs that are effective against increasingly resistant viruses.

However, for patients with multidrug-resistant HIV-1 whose viral load cannot be suppressed, there is an option of continuing treatment with the best-tolerated and least-toxic combinations. This compromise approach—minimizing toxicity when maximum viral suppression is no longer possible—prolongs survival and increases

Partial Virological Responses After Virological Failure



In some patients receiving treatment, resistance to drugs allows the level of virus to rebound. Partial virological responses after virological failure are due to continued activity of the drugs and selection for viruses with poor replication capacity.

the quality of life until more effective therapies appear. In other words, suppressing the virus to undetectable levels is the ideal, but living with a lower level of viral replication is an acceptable alternative for many patients who are awaiting the development of new classes of drugs.

Early concerns that drug resistance would completely offset the therapeutic benefits of modern drug therapy and would spread like wildfire have been modulated by hard-won evidence from studies supported by Dr. Grant and his collaborators. Clinical studies have provided evidence that continued combination therapy in the face of drug resistance is better than no therapy at all. Epidemiological studies have indicated that transmitted, or primary, drug resistance is not increasing over time and may be decreasing in some communities, such as San Francisco, where antiviral treatment is widespread.

The finding of impaired viral fitness in drug-resistant infections has allayed concerns that greater availability of antiretroviral drugs for developing countries would lead to a second epidemic fueled by drug-resistant viruses. Spurred by desperate need and a growing appreciation that treatment responses are robust, international funds have been made available in the past 3 years to establish treatment clinics, which now provide therapy to 12% of those who need it around the world. Much has been accomplished, but clearly much more remains to be done.

Much More to Learn and Do

The widely publicized “New York Case” demonstrated that multidrug-resistant HIV-1 can be highly virulent and transmitted. Although the convergence of full virulence and multidrug resistance remains rare, we have learned never to say “never” with respect to HIV-1 evolution: high replication rates combined with high mutation rates conspire to give this virus many avenues to adapt to new circumstances.

Work in Dr. Grant’s laboratory aims to determine if there are therapeutic opportunities for lowering the viral mutation rate, which would impede the appearance of drug-resistant viruses and viral escape from immune responses. In the meantime, epidemiological and clinical virological research is urgently needed to determine if HIV-1 is increasing in drug resistance and virulence at this new stage of the epidemic.

Gladstone investigators will continue to build partnerships with local biotechnology firms and public health agencies to assure that the best possible clinical and epidemiological research is done. This research aims to stay ahead of the virus, or better yet, to find new therapies and prevention strategies that can head HIV evolution off at the pass.