Daniel Douek - MD, PhD
Chief, Human Immunology Section
Vaccine Research Center (VRC) – Bethesda

Dr. Daniel Douek

Dr. Douek studied medicine at the Universities of Oxford and London, receiving academic scholarships from both institutions. He then practiced internal medicine and became a Member of the Royal College of Physicians (London) in 1993. He was awarded a Wellcome Trust Clinical Graduate Training Fellowship to pursue a Ph.D. in immunology at the University of London, which he earned in 1997. He completed his postdoctoral work at the Rockefeller University and the University of Texas Southwestern Medical Center, Dallas, where he was named assistant professor in infectious diseases (2000). While a postdoctoral fellow with Dr. Richard Koup, he developed the "TREC assay" to measure thymic output in humans. Dr. Douek was appointed to a tenure-track position in the VRC Laboratory of Immunology in November 2000. Dr. Douek brought impressive academic credentials, training, and experience to the VRC and is internationally recognized in the fields of basic immunology, HIV, and transplantation biology. He was converted to a tenured senior investigator position in February 2007, the year in which he was presented with the World AIDS Day Award. He serves as chief of the Human Immunology Section at the VRC.

Benefits of Antiretroviral Therapy are:

- **Reduction in Mortality and/or AIDS-Related Morbidity According to Pretreatment CD4 Cell Count**
- **Effects of Viral Replication on HIV-Related Morbidity**
- **Since the mid-1990s, it has been known that measures of viral replication predict HIV disease progression.**

- **Among untreated HIV-infected individuals, time to clinical progression and mortality is fastest in those with higher viral loads.**
- **This finding is confirmed across the spectrum of HIV-infected patient populations, such as injection drug users (IDUs), women, and individuals with hemophilia.**
- **Several studies have shown the prognostic value of pre-treatment viral load for predicting post-therapy response.**
- **Once therapy has been initiated, failure to achieve viral suppression and viral load at the time of treatment failure are predictive of clinical disease progression.**

More recent studies have examined the impact of ongoing viral replication for both longer durations and at higher CD4 cell counts. Using viremia copy-years, a novel metric for quantifying viral load over time, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort found that cumulative exposure to replicating virus is independently associated with mortality. Using viremia copy-years, the HR for mortality was 1.81 per log10 copy-year/mL (95% CI, 1.51–2.18), which was the only viral load-related variable that retained statistical significance in the multivariable model (HR 1.44 per log10 copy-year/mL; 95% CI, 1.07–1.94). These findings support the concept that unchecked viral replication, which occurs in the absence of effective ART, is a factor in disease progression and death independent of CD4 count.
The EuroSIDA collaboration evaluated HIV-infected individuals with CD4 counts >350 cells/mm3 segregated by three viral load strata (<500 copies/mL, 500–9,999 copies/mL, and ≥10,000 copies/mL) to determine the impact of viral load on rates of fatal and nonfatal AIDS-related and non-AIDS-related events.
The lower viral load stratum included more participants on ART (92%) than the middle (62%) and high (31%) viral load strata. After adjustment for age, region, and ART, the rates of non-AIDS events were 61% (P= 0.001) and 66% (P= 0.004) higher in participants with viral loads 500 to 9,999 copies/mL and >10,000 copies/mL, respectively, than in individuals with viral loads <500 copies/mL. These data further confirm that unchecked viral replication is associated with adverse clinical outcomes in individuals with CD4 counts >350 cells/mm3.
Collectively, these data show that the harm of ongoing viral replication affects both untreated patients and those who are on ART but remain viremic. The harm of ongoing viral replication in patients on ART is compounded by the risk of emergence of drug-resistant virus. Therefore, all patients on ART should be carefully monitored and counseled on the importance of adherence to therapy.

Effects of Antiretroviral Therapy on HIV-Related Morbidity:
HIV-associated immune deficiency, the direct effects of HIV on end organs, and the indirect effects of HIV-associated inflammation on these organs all likely contribute to HIV-related morbidity and mortality. In general, the available data demonstrate the following:

- **Untreated HIV infection (ongoing viral replication) may have negative effects at all stages of infection.**
- **Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.**

- **ART is beneficial even when initiated later in infection; however, later therapy may not repair damage associated with viral replication during early stages of infection.**
- **Sustaining viral suppression and maintaining higher CD4 count levels, mostly as a result of effective combination ART, may delay, prevent, or reverse some non-AIDS-defining complications, such as HIV-associated kidney disease, liver disease, CVD, neurologic complications, and malignancies, as discussed below**

Persistent Inflammation and Immunodeficiency During Antiretroviral Therapy:
Untreated HIV infection is associated with chronic inflammation, as defined by the frequency of activated T cells and monocyte/macrophages and levels of a number of pro-inflammatory cytokines (e.g., IL-6, CRP, soluble CD14). Effective ART decreases levels of most of these inflammatory markers, but the effect is often incomplete, with levels in many of those on ART remaining higher than those observed in age-matched uninfected adults.

Chronic inflammation during both untreated and treated disease is strongly associated with risk of non-AIDS defining morbidity and all-cause mortality:
Because HIV replication contributes to this inflammatory state through both direct and indirect mechanisms, earlier use of ART to blunt this process may be beneficial. However, there are no data showing that ART-mediated changes in any inflammatory biomarker are associated with reduced morbidity and mortality.

Immune function as defined by the peripheral CD4 cell count is also an important determinant of health:
Although effective ART results in a sustained and beneficial increase in CD4 cell counts, this effect is often incomplete. Patients who delay therapy to the point of advanced immunodeficiency may require several years of ART to normalize their peripheral CD4 cell counts, and some patients may never achieve a normal level.

A lower CD4 count on therapy is associated with higher risk of developing cancer, liver disease, cardiovascular disease and death:
In some studies a history of low CD4 counts is associated with risk of morbidity and mortality during subsequent effective therapy.
Collectively, these observations support earlier use of ART. Treatment decreases the level of inflammation, which may be associated with reduced short-term risk of AIDS- and non-AIDS-related morbidity and mortality.
ART also prevents progressive loss of CD4 cells, thus reducing risk of immunodeficiency and its related complications. Some studies have shown that a patient's pre-therapy CD4 cell count nadir is predictive of the degree of residual inflammation and/or T-cell dysfunction during ART.
Thus, earlier ART may result in less residual immunological perturbations during treatment, which theoretically may result in reduced risk of disease during the decades that a patient requires ART (CIII).

Stefano Rusconi:

We are here with Dr Danny Douek, a very prominent investigator into HIV and immunology, working presently at NIH, Bethesda. So, one question but a very provocative yet clear. So Danny, what's still against an early initiation of Haart.

Dr Douek:

In my opinion, nothing. Think about it this way: we have an infectious, communicable disease with essentially 100% mortality, and for some reason, we decide not to treat everybody with treatment that is, let's say, 100% effective. Ok. Why are we in this situation? We're in this situation because a number of years ago when we first develop these drugs, they were unpleasant, difficult to take, lots of side effects, really quite toxic. We are not in that situation any more. Of course, they are drugs, and there are side effects, but the number of side effects, the toxicity of the drugs and the difficulty of the regimens to actually take these drugs is getting less and less and less. And at the moment, I think we're in the situation where we should be treating everyone because it's a communicable disease with 100% efficacious treatment and it has 100% mortality. It's as if we were to say, perhaps we should wait to treat diabetics until they're really quite sick rather than when they need insulin. In my mind, I think that's a reasonable comparison to make. So as far as I'm concerned, that's the infectious-disease argument for treating immediately. There's another argument for treating immediately, which is the argument of pathogenesis that we know that the virus begins to cause damage to the immune system immediately. And I would say by the end of the first month after infection, to a certain degree it's game over. The reservoir is seeded; the CD4 T cell pools are extremely depleted, and you begin the destructive cycle of immune activation, which continues to destroy the rest of your body systemically, not just immunologically. So there is a transmission argument for instituting therapy immediately, there's pathogenesis argument for instituting therapy immediately. And in terms of side effects, they're getting less and less and I think it's easier for the patients to take those drugs. I think one could probably make a cost argument as well - although I'm not sure what the cost argument is, in terms of long-term treatment of complications from untreated HIV infection. So that's where I stand at the moment. I think the difficulty that we are faced with is defining early treatment. If we really want to make a big effect on the pathogenesis, we're talking about very, very early treatment in Fiebig stage I, Fiebig stage II. By Fiebig stage IV or V, it's probably over. So I think we're at a situation now where, cost aside, we should be trying to test as many people as possible, find out who's infected, and treat everyone when we find out that they're infected. That's my view.

People in poor countries tend to have less access to health services than those in better-off countries, and within countries, the poor have less access to health services. Although a lack of financial resources or information can create barriers to accessing services, the causal relationship between access to health services and poverty also runs in the other direction. When health care is needed but is delayed or not obtained, people's health worsens, which in turn leads to lost income and higher health care costs, both of which contribute to poverty. Deprivations that lead to ill health are common in developing countries, and the poor in developing countries are particularly at risk.
The relationship between poverty and access to health care can be seen as part of a larger cycle, where poverty leads to ill health and ill health maintains poverty.
Here we review factors that affect access to health services in developing countries, focusing on the role of poverty. We then explore some ways that innovations in the delivery and

financing of health care in developing countries could improve access to the poor.
The relationship between poverty and health care is a common subject of research and policy, often using different definitions of poverty and health care access. Although a detailed discussion of the meaning of poverty is beyond the scope of this article, poverty is recognized as extending beyond the concept of deprivation of income or material assets. It also can be understood as the lack of freedom to lead the life people have reason to value, with people and communities empowered to lead healthy lives seen as both a means to overcoming poverty and an end in itself.
In this context, public health and clinical health services, along with food, water, sanitation and other human assets, such as knowledge and education, can be considered necessary material conditions for good health.
Empowerment at the individual level affects individual choices over healthy lifestyles and choice of health services, whereas at the community level, empowerment involves the securing of resources for health and health services. Absolute levels of income and material deprivation influence people's risk of disease and ability to purchase health services, though relative socioeconomic position also matters. Sen argues that relative income is important because it translates into capabilities, or what you are able to do with what you have, which is an important factor in accessing health services.
By either approach to defining poverty inequalities, there is a general consensus that they are associated with unjust differences in both constraints and opportunities to make choices over health care.
Lost income and health care payments further result in shocks that adversely affect income and asset inequalities, as well as other dimensions of poverty.
We will consider both absolute and relative assessments of poverty, noting that the ethical perspective or specific question being asked will inform which way of examining poverty is more appropriate.
There are also many definitions of access to health services, with most researchers recognizing that access is related to the timely use of services according to need.
Although some researchers distinguish between the supply and opportunity for use of services and the actual using of health services, most view access to health services as including realized need.
Here we use a conceptual framework that builds on longstanding descriptions of access to health services that includes actual use.
In this framework, four main dimensions of access are described, each having a supply-and-demand element, and include the following:

1. Geographic accessibility—the physical distance or travel time from service delivery point to the user
2. Availability—having the right type of care available to those who need it, such as hours of operation and waiting times that meet demands of those who would use care, as well as having the appropriate type of service providers and materials
3. Financial accessibility—the relationship between the price of services (in part affected by their costs) and the willingness and ability of users to pay for those services, as well as be protected from the economic consequences of health costs
4. Acceptability—the match between how responsive health service providers are to the social and cultural expectations of individual users and communities.

Despite improvements in providing access to health care in developing countries, substantial proportions of their populations have limited access. The poor in these countries suffer from a disproportionate burden of disease yet usually have less access to health care, whether measured by geographic accessibility, availability, financial accessibility, acceptability, or quality of care. However, recent studies show that this outcome is not inevitable. Success depends in part on gaining a local understanding of the dimensions and determinants of access to health services, along with determined attempts to improve services for the poor.
There are many innovations in financing, service delivery, and regulation of care that hold promise for improving access for the poor. The same can be said of older strategies. In either case, the challenge remains to find ways to ensure that vulnerable populations have a say in how strategies are developed, implemented, and accounted for and to ensure that information and incentives are aligned in ways that can demonstrate improvements in access by the poor.

Stefano Rusconi:

In this respect, do you see any potential difference between the so-called underdeveloped countries and more industrialized countries like the US or Europe?

Dr Douek:

Well, obviously, there's the problem of finance, of money, because the underdeveloped countries, the developing nations, don't have budgets as big as our countries. But people in those countries are pretty much the same as people in our countries, and personally I think we should treat them in exactly the same way and give them the availability. Perhaps even more so, you know, because their healthcare systems are not as developed as our healthcare systems and so the consequences of long-term untreated HIV infection in terms of the society and the workforce in those countries may be even more detrimental than it is in our countries. And so, I think we should be even more focused in treating in the developing nations.

Stefano Rusconi:

Ok. Thank you, Danny