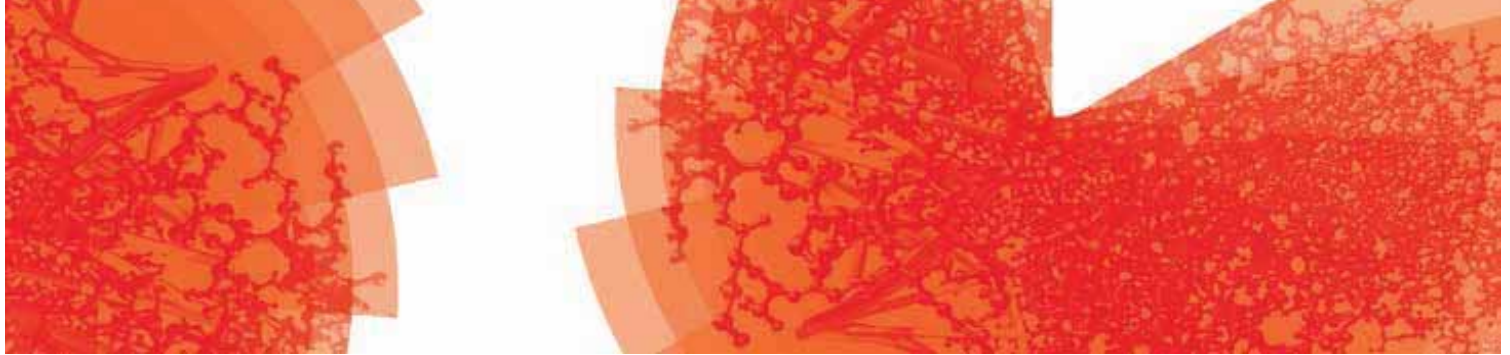


# Opening doors to HIV discovery



Challenges surrounding HIV research are constantly evolving. **Dr Robert Shafer** discusses how he handles the difficulties embedded in treating this infectious disease and explains the ways he encourages scientists to work more closely towards advancing research efforts

## Can you begin by commenting on the response to HIV treatment and containment?

HIV treatment programmes have saved millions of lives, prevented millions of infections and restored hope to the populations that have been hardest hit by the pandemic. However, the challenge of treating HIV is staggering. There are 35 million infected persons worldwide – most of whom are in resource-limited settings – and nearly 2 million new infections occur each year. Although 15 million individuals are receiving treatments, this number must continue to grow to keep those who are already infected healthy, prevent infected people from transmitting HIV and keep pace with new infections. Despite the many advances that have been made, maintaining the status quo will not contain the pandemic.

## What inspired you to set up the Stanford HIV Drug Resistance Database (HIVDB)?

In the late 1990s, I was sequencing reverse transcriptase and protease genes of HIV strains from patients in clinical trials. I realised that I could better understand my findings if I examined them in the context of previously published sequences from other researchers, so I began a relational database that linked these sequences to the treatments of the patients from whom the sequenced viruses were obtained.

When drug susceptibility testing became more common, I also linked sequences to these results on sequenced viruses. Because this process was arduous, I published the database on the web so that other researchers would not have to repeat this work. The timing was perfect

because the late 1990s saw the development of many new drugs, including nonnucleoside reverse transcriptase inhibitors and protease inhibitors. It had become too difficult to keep track of which HIV mutations were natural variations and which ones were selected by drugs. It also became difficult to determine the relative effects of different mutations on the various reverse transcriptase and protease inhibitors.

## How do you monitor and uphold the validity and reputation of the website?

The vast majority of published studies are valid; the main challenge is that the results from an individual study can be misinterpreted if they are taken out of context or represented in a database inappropriately. We address this by organising HIVDB around data relationships that lend themselves to specific meta-analyses. These meta-analyses have two benefits: first, they allow us to recruit data that authors might not ordinarily make publicly available; and second, they force us to rigorously examine those data in HIVDB.

## Why is the debate on open access critical to the future of bioinformatics research?

Publicly available databases are integral to life sciences research. In many fields there is a strong culture of data sharing. Genomics researchers, for example, religiously submit the raw data in their studies to public databases. But data sharing is uncommon in medical fields where researchers often treat data as a private preserve. Many expert panels and funding agencies have published guidelines underscoring that the raw data described in

a published paper should be made publicly available so that other researchers can validate the published findings and reuse the data to promote discovery. Despite this, there is no mechanism for ensuring adherence to these guidelines. Obtaining data from published studies is an ongoing challenge.

## In 2013, you received the Clinical Virology Award by the Pan American Society for Clinical Virology. On a personal level, what was the significance of this award?

This was very meaningful to me because each of the previous awardees were highly accomplished and because there are currently so many outstanding clinical investigators studying human viral diseases. Additionally, the award meant that the Society recognised the value of the database and accompanying decision support tool, which are not traditional types of medical research.

## What do you see as critical challenges for HIV treatment in the next few years, and how will your research and HIVDB help overcome them?

Three types of advances are needed: better treatments, better laboratory monitoring and better education of researchers, public health officials and care providers in resource-limited settings. HIVDB is a natural fit for addressing the educational challenge. HIVDB is also being used to guide the development of diagnostics such as inexpensive point-of-care drug resistance assays for the regions most affected by resistance. Finally, HIVDB provides insight into which HIV treatments are less prone to drug resistance and virological failure.

# The power of sharing knowledge

An online collaborative platform known as the **Stanford HIV Drug Resistance Database** is helping to improve treatment options for patients by making antiviral drug resistance data freely available

**THE ORIGINS OF** the human immunodeficiency virus, better known as HIV, can be traced back to Africa, where the disease has been found in non-human primates and is believed to have been transferred to humans through zoonosis sometime in the early 1900s. However, it was not until the 1980s that the scientific community first identified the virus in humans when cases of AIDS started to appear. Rapidly, AIDS turned into an epidemic, became a pandemic and has now killed more than 30 million people worldwide.

Fortunately, the number of HIV/AIDS deaths has been steadily dropping over the past decade, thanks in large part to significant efforts made to develop effective antiviral drugs and establish national HIV treatment programmes. However, with over 35 million people still living with the infection and up to 2 million new yearly infections, it remains a significant global problem.

There are many challenges when it comes to finding viable treatment options for such a complex and widespread condition like HIV/AIDS. This undertaking is further complicated by the fact that viruses can change form and develop resistance to drugs over time – essentially rendering once successful treatment regimens ineffective. Resistance to antiviral drugs is becoming more common, and treatment failure and drug resistance occur in about 10 per cent of treated patients each year.

## A SHARED EXPERIENCE

One researcher who is well-versed in the issue of drug resistance in HIV infected patients is Dr Robert Shafer. His postdoctoral work centred on infectious diseases, studying HIV, tuberculosis and their shared role in the rising prevalence of multidrug-resistant tuberculosis.

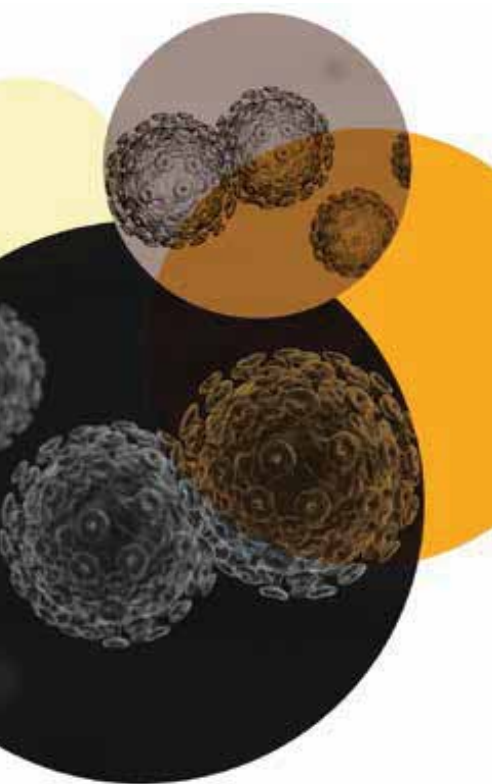
Now based at Stanford University in California, USA, his research focuses on influencing HIV/AIDS treatment and prevention guidelines by pinpointing the root causes of the emergence and spread of drug resistance. When the pace of HIV drug development quickened in the mid-1990s, Shafer scoured published papers in the GenBank database to determine which HIV mutations developed in patients receiving each HIV drug. He also quantified the effect of each of these mutations on the drug that the patients were treated with and other drugs

belonging to the same class. In 1999, this work formed the foundation for the Stanford HIV Drug Resistance Database (HIVDB), which has grown over the past two decades, and is storing, analysing and making freely available the raw data underlying current knowledge about HIV drug resistance.

## HIVDB: A VALUABLE RESOURCE

When Shafer first worked in this area, HIV drug resistance seemed inevitable and challenged the hope that effective therapies for HIV could be developed. During the past 20 years, the importance of HIV drug resistance has taken on new meaning. Great strides in antiviral drug development have led to many effective treatments. Unprecedented collaboration between public health officials, political leaders and global funders has led to the successful use of these treatments by millions of individuals worldwide. Now, the study of drug resistance encompasses developing strategies to minimise the emergence and spread of drug resistance so that the dramatic scientific and public health accomplishments of the past 20 years continue.

Over the years HIVDB has served as a valuable resource for researchers, healthcare organisations and clinicians, helping to facilitate several large collaborations on the molecular epidemiology of drug resistance. Many independent researchers routinely use the database to identify gaps in the medical literature on HIV drug resistance. Drug developers have used the database to determine the extent of cross-resistance between the drugs they are producing and drugs of the same class that are already in use in the clinic. HIVDB has become part of the fabric of HIV drug treatment research, as Shafer describes: “The data in HIVDB have helped standardise the approach to



## A FIGHT FOR HIVDB

In 2008, Shafer and the HIV Drug Resistance Database faced a vexing obstacle: legal action from Advanced Biological Laboratories (ABL), a clinical software and information company that claimed the database infringed one of its patents. Stanford University initially signed a cross-licensing agreement with ABL, intending to put the HIV community on notice about its patents and to limit the use of the database; however, by 2010, the Stanford University Provost publicly acknowledged that this agreement had been a mistake and reiterated Stanford’s support for open access to the database ([http://bit.ly/HIVDB\\_Provost](http://bit.ly/HIVDB_Provost)). This affair was eye-opening to Shafer and to other faculty at Stanford, many of whom rallied to his side. The American Association of University Professors – which had not previously involved itself with intellectual property matters – also eventually weighed in ([http://bit.ly/HIVDB\\_AAUP](http://bit.ly/HIVDB_AAUP)). In 2012, ABL’s patents were invalidated and all elements of its agreement with Stanford were nullified.

global HIV-1 drug resistance surveillance and to quantify drug resistance levels in clinical trials and cohort studies”.

## ANALYSE THIS

In addition to hosting raw data, the HIVDB website also provides several virus sequence analysis programs to help users, particularly healthcare providers, interpret the information available to them. This is a very valuable tool as interpreting the result of genotypic drug resistance tests is a very complex task. “There

## INTELLIGENCE

### STANFORD HIV DRUG RESISTANCE DATABASE

#### OBJECTIVES

- To collect, analyse, and make available the diverse forms of data underlying HIV drug resistance knowledge
- To provide a resource for care providers treating patients with HIV infection and scientists studying HIV treatment

#### KEY COLLABORATORS

**Dr Jose Luis Blanco**, University of Barcelona, Spain • **Dr Jeffrey Fessel**, Kaiser Permanente Medical Care Program, USA • **Dr Stephen Hart**, Frontier Science & Technology Research Foundation, USA • **Dr Michael Jordan**, Tufts University, USA • **Dr David Katzenstein**, Stanford University, USA • **Dr Anna Kolomeets**, Omsk Research Institute of Natural Focal Infections, Russia • **Dr Tulio de Oliveira**, University of KwaZulu-Natal, Durban, South Africa • **Dr Jonathan Schapiro**, Israeli National Hemophilia Center, Israel • **Dr Celia Schiffer**, University of Massachusetts Medical School, USA • **Dr Anne-Mieke Vandamme**, University of Leuven, Belgium • **Dr Gert van Zyl**, National Health Laboratory Service, Tygerberg, South Africa • **Dr Susan Holmes**, **Dr Vici Varghese**, Stanford University, USA • **Dr Chunfu Yang**, Centers for Disease Control and Prevention, USA

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**ROBERT SHAFER** studied at Columbia University for his BA in Premedical Sciences before receiving his MD from New York University in 1983. He began his

research on infectious diseases during postdoctoral training at Kings County Hospital, New York. Subsequently, he started a clinical virology fellowship at Stanford University, and in 1999 created the HIV Drug Resistance Database.



**SOO-YON RHEE** is Director of the HIV Drug Resistance Database. Since 2000, she has been responsible for expanding the database to meet the needs of its growing research

community. She is currently studying for her PhD in Biomedical Sciences at the University of Leuven, Belgium, supervised by Dr Anne-Mieke Vandamme and Dr Robert Shafer.



Global summary of viruses from more than 50,000 people in nearly 300 studies of transmitted HIV drug resistance from 2000-13. Transmitted resistance refers to resistance in individuals who were never treated and were likely infected by a virus that developed resistance in a different person. Individuals with transmitted resistance are at increased risk of virological failure when treated with an initial drug regimen. Global rates range from below 5 per cent in regions where drug therapy has recently been introduced, to as high as 15-20 per cent in regions where drugs have been available for 20 or more years. The shade of red becomes more pronounced as the levels of resistance increase. The size of the circles are proportional to the size of the individual studies.

are more than 200 drug resistance mutations that cause varying levels of resistance to the roughly 15 commonly used antiretroviral drugs," Shafer explains. "Further complicating the picture is the fact that HIV exists within an individual as a mixture of innumerable but genetically related variants – not all of which are detectable by standard sequencing."

To simplify this work, HIVDB features an HIV-1 drug resistance interpretation program called Sierra. "It is a highly transparent,

rules-based expert system that takes into account an extensive amount of published literature. The program contains several hundred mutation penalty scores and about 250 comments. The transparency of the program helps educate users – and us who work on it, because we constantly receive feedback that allows us to improve the interpretation system," Shafer explains.

Users – who include clinicians, clinical and public health laboratories, and HIV care providers – can submit a sequence to Sierra and the program will predict which antiviral drugs are likely to be most active against the virus. They can also use the service to interpret the results of genotypic drug resistance tests from patients. Moreover, Shafer is happy to accommodate users' specific needs by providing exact forms of output tailored to their work.

To date, the Sierra service has been well received, having been integrated into the World Health Organization (WHO)'s HIV drug resistance network, the National Institutes of Health (NIH)-funded AIDS Clinical Trial Group, and several hundred research and clinical laboratories worldwide.

#### DATA ON TRIAL

It is clear that openness and willingness to share data is at the heart of what has made HIVDB such a successful and powerful tool. "Data are the most important commodity in science, and their management is of critical importance to knowledge discovery and patient care," Shafer affirms. "HIVDB is one of the highest profile demonstrations that sharing and aggregating raw data from many studies generates new knowledge that cannot be obtained from individual studies."

#### PLANS FOR IMPROVEMENT

The database is a valuable tool for the thousands of people who access it each month, but Shafer recognises that HIVDB can be further developed to reach an even wider audience. In particular, he would like to target individual care providers, especially those who have limited knowledge about HIV drug therapy and resistance. "To address this, we are working to extend HIVDB to include many additional published studies even if the raw data from these studies are not publicly available," Shafer highlights. "We are also creating a version of the HIVDB interpretation program that will be able to take into account a patient's treatment history as well as a patient's virus sequence."

