When he was an intern in New York City in 1980, Dr. Richard Marlink knew something was going on, he just didn’t know what. The hospital where he worked, St. Vincent’s, served patients from Harlem to Greenwich Village. “Mainly gay men, homeless people, and drug addicts used our clinics,” said Marlink. The staff began seeing a surprising number of rare conditions like Kaposi’s sarcoma and miliary tuberculosis—conditions usually seen only once or twice in a medical career.

In 1981, the CDC published an account of five gay men in Los Angeles with a rare form of pneumonia. The report was later acknowledged as the first scientific mention of AIDS. In retrospect, it’s clear that Marlink and his colleagues at St. Vincent’s had been treating some of the first AIDS patients. Thirty years later, Marlink would be responsible for putting more AIDS patients on treatment than almost anyone on the planet.

Richard Marlink, or Ric as his friends call him, grew up in Colorado and New Mexico. As a child, he visited his great uncle, Dr. Brownie Farrand, in the small town of Jordan, Montana. The only doctor in the county, Farrand dealt with everything from broken legs to eye glasses. Ric admired the way he talked to patients, learned their stories, and cared for them completely. From his great uncle’s example, Ric decided to become a doctor, too.

(continues on page 4)
Your background is as an infectious disease doctor. How did you get involved with cost-effectiveness research?

I have a strong math background from college. When I was pursuing my MPH (HSPH '01), I took Milt Weinstein’s course in Decision Science. It was mathematically oriented and I loved it. Infectious diseases are among the diseases frequently modeled, so it was a perfect fit.

What is cost-effectiveness?

By definition, cost-effectiveness is a ratio. It is costs in the numerator divided by effectiveness in the denominator. Generally, we talk about effectiveness in terms of life expectancy, so the units of the ratio are dollars per year of life saved.

QALY (quality-adjusted life year) is based on the number of years of life that would be added by an intervention. Each year in perfect health is assigned the value of 1.0, down to a value of 0.0 for being dead. If the years would not be lived in full health, for example if the patient has chronic dementia or paralysis, then the years are given a reduced value between 0 and 1 to account for the diminished quality of life.

Once you have a ratio, the next question is, how would you know an attractive ratio if you saw one? What are we, as a society, willing to pay in dollars for a year of life saved?

The history of this question dates back to hemodialysis for those in chronic renal failure. We, as a society, are willing to pay for long-term dialysis in those with chronic kidney disease. It follows, then, that we should be willing to pay for other medical interventions that are “cheaper” (on a dollars per year of life saved basis) than dialysis.

A study in the early 1990s suggested that the incremental cost-effectiveness ratio of hemodialysis, compared to no dialysis, was about $50,000 per QALY. This ratio quickly became a benchmark. Any intervention with a cost-effectiveness ratio less than $50,000/QALY should also be considered an economically attractive one.

Over the years, because of inflation and new technologies, healthcare became more expensive. People started asking why everything was going up except our willingness to pay for health. Over time, our “willingness to pay” ratio in the United States has generally increased. Now that ratio is felt to be around $100,000 to $150,000 per QALY.

How does cost-effectiveness translate to value in international settings, especially resource-poor countries in Africa?

Policy makers needed to decide what a reasonable value was in international settings. The World Health Organization (WHO) convened a committee that provided guidance based on the relative wealth, or per capita Gross Domestic Product (GDP), of a country.

What are we, as a society, willing to pay in dollars for a year of life saved?

If the incremental cost-effectiveness ratio of an intervention in $/DALY (disability-adjusted life year) is less than the per capita GDP of a country, it may be considered very cost-effective. If it is less than three times the per capita GDP of a country, it may be considered cost-effective.

In the case of the U.S., our per capita GDP is about $48,000. Under WHO guidance, then, an intervention with an incremental cost-effectiveness ratio less than $48,000 per QALY might be considered very cost-effective; less than $140,000 per QALY might be considered cost-effective.
In international settings, this brings up large ethical issues. The per capita GDP in South Africa is about $8100, which sounds low when compared to the U.S., until you look at a country like Mozambique, where the per capita GDP is about $530.

And should one really be using an individual country's own GDP as a benchmark for “willingness to pay” when there are outside partners helping to finance care? When the World Bank finances an intervention in South Africa and Mozambique, should they finance more in South Africa than Mozambique because South Africa’s GDP is higher? There are a lot of ethics around this, but those are the benchmarks often discussed.

The HPTN052 study in 2011 showed that treatment of HIV with antiretroviral therapy (ART) also prevents the spread of HIV. How does that change the cost-effectiveness equation of large-scale ART programs?

We—Ken Freedberg and I and the entire Cost-Effectiveness of Preventing AIDS Complications (CEPAC) team—have partnered with the HPTN052 team. We presented data at the International AIDS Society in 2012 examining the cost-effectiveness of treatment as prevention. We looked at two countries, South Africa and India. We believe the cost structure is different in those two countries and certainly the per capita GDPs and benchmarks are different. In our analyses, we showed that treatment as prevention is very cost-effective in both South Africa and India over lifetime horizons.

It's important to highlight that the question of the cost-effectiveness of treatment as prevention and the question of the cost-effectiveness of test and treat are different. Treatment as prevention implies that you have somebody in front of you with HIV and a high CD4 count [indication of strength of immune system] and the question is, do you provide ART to that person now, or do you wait until s/he might otherwise meet WHO treatment criteria? In a test and treat analysis, you have to test many people to find that same person. There are a lot of resources and costs that must be considered when an additional prerequisite is to identify the pool of people who might merit early treatment.

Perverse things will happen if we look at cost-effectiveness alone. It’s one of the tools, and I think a much-ignored tool, to help guide us in making decisions.

Does providing ART for people with HIV save money?

Policy makers do not necessarily want to hear that an intervention is cost-effective; they want to hear that it is going to save money. Almost none of our analyses demonstrate that we save money. Why? Our work is about keeping people alive, and the longer people live, the more they cost. Sadly, dying is cheap and staying alive costs more.

In treatment as prevention, we will be treating people who have HIV. The wonderful news is that this treatment will allow them to live longer. When they live longer, they will need ART for longer because there is no cure for HIV. They will need ART for the duration of their lives. There are many millions of people for whom that is true.

We will also, fortunately, be averting infections down the line. For those people—yes—we will save money. Will the money saved offset the current cost of the ART that it will require to save that money? I suspect not.

With limited resources, how do we decide where to spend them? Does cost-effectiveness give us clear answers?

Perverse things will happen if we look at cost-effectiveness alone. It’s one of the tools, and I think a much-ignored tool, to help guide us in making decisions.

What it tells you is whether an intervention is worth paying for. Is this good value for money compared to other things possible or compared to things you’re already paying for? What it doesn’t tell you is if the intervention is affordable. Something may be good value for the money, but you still may not have the money to pay for it.

My work is focused in the U.S. and resource-limited settings to help people decide what to do when resources are really limited. There is a huge menu of things that we could do. All is not possible. My goal is to maximize human life with those limited resources that we have. This is one way of doing it.
Twenty years later, Ric found himself in Boston as an oncology fellow at New England Deaconess Hospital. Oncology was a good fit because it covered all aspects of a patient’s health, managing problems that arose from having cancer and having to undergo harsh treatments to eradicate it. It was the mid 1980s. Ric was married and had just become a father.

Ric helped set up the first AIDS clinic in Boston, which consisted of a small exam table in a hospital utility closet. Little was known about AIDS at the time and fear and stigma were rampant. His patients were mostly gay men. Many of them had Kaposi’s sarcoma or other AIDS-related cancers.

“In the early days of AIDS, many of us were oncologists,” said Ric. Oncologists were used to caring for very sick people. The early AIDS drugs, like cancer chemotherapy, had harsh side effects. They were also ineffective. In the 1980s, most AIDS patients died.

When the head of his department, Dr. Jerome Groopman, suggested that he get some lab experience, Ric visited Dr. Max Essex at the Harvard School of Public Health. In the Essex Lab, Ric met an energetic post-doc named Dr. Tun-Hou Lee. Working with Essex, Lee had already made a number of important findings about the AIDS virus. “His excitement at discovery was infectious,” said Marlink, who quickly joined the team.

It was an exhilarating, exhausting time in AIDS research. Essex, his graduate student Dr. Phyllis Kanki, and colleagues discovered a second AIDS virus, HIV-2, in West Africa. Ric was on the team sent to Senegal to investigate. In Dakar, he examined prostitutes who were infected with HIV-2. He helped establish a study of sex workers to learn what problems the new AIDS virus caused in humans. “It was invaluable to have someone who could identify with the concerns of patients, especially from the physician/patient relationship,” said Essex.

The working conditions in Africa were difficult. Trained doctors and nurses were scarce and medical supplies were often nonexistent. In spite of these obstacles, Ric found the work rewarding. “A little bit can go a very long way in Africa,” he said.

The Harvard AIDS Institute (HAI) was established in 1988. Ric became Executive Director in 1992, a position he still holds. His mission, as he sees it, is to bring together people from different areas of public health to end AIDS globally. “Ric is extremely effective at connecting people,” said Essex. “He excels at raising questions and stimulating discussions among people from a wide variety of backgrounds.”

Over the past 20 years, Ric has created or led a number of important initiatives. In 1996, he was instrumental in organizing the Leading for Life Summit that brought African-American leaders to Harvard to respond to the AIDS crisis. In 1998, he created the Enhancing Care Initiative to improve clinical care for people living with HIV/AIDS in Brazil, Puerto Rico, Senegal, South Africa and Thailand. In response to the shortage of trained healthcare workers in Africa, he led the creation of the KITSO AIDS Training Program in 2000. To date, KITSO has trained over 9,000 healthcare workers.

From 2004 to 2012, Ric directed the HSPH PEPFAR program in Botswana, which helped the government place over 150,000 people on AIDS treatment. At the same time, he was the Principal Investigator of the Elizabeth Glaser Pediatric AIDS Foundation’s PEPFAR program which provided AIDS treatment to over 560,000 people in five other African countries.

Recently, Ric has led several studies to determine the best and most cost-effective models of AIDS treatment delivery in southern Africa. He co-taught a course at HSPH on Combating Infectious Diseases in Developing Countries. In 2011, he organized the AIDS@30 Symposium in Boston. You get the idea.

With so much of his time spent on conference calls and global travel, Ric Marlink still considers himself—like the great uncle who inspired him—a clinician. His job, he’ll tell you, is to improve healthcare for AIDS patients in poor settings. Only now, rather than treating several patients each day, his work impacts the lives of tens of thousands.
Models of Care
Good Grades and Unanswered Questions

It's a matter of life and death. Say there are two brothers in their early 30s. Both become infected with HIV at around the same time and both have about the same CD4 level, a measure of how well one's immune system is working. One brother remains in his village near the Kalahari Desert to help with the family farm and cattle post. The other moves to Botswana's capital, Gaborone, to work in an office. Both men are treated with the same AIDS drugs under the country's national treatment program. Yet depending on where they get treatment, one brother has a ten times greater chance of dying than the other. Why?

In Botswana, the HIV prevalence among adults aged 15 to 49 is 25%, the second-highest rate in the world, behind only Swaziland. To address this epidemic, Botswana created a national antiretroviral treatment (ART) program in 2001 to provide free, life-saving drugs to all eligible citizens. After initial delays, the number of patients increased quickly and the program expanded to increasingly rural areas. Because of the fast growth, it was important to monitor and evaluate the results. HAI played a significant role in this process.

"As you're building a large, new program, it's hard to have everything run well," said Dr. Richard Marlink, Executive Director of the Harvard AIDS Initiative (HAI). Marlink was the Principal Investigator of the Models of Care project that evaluated the 2002 to 2010 scale-up of Botswana's national program. His team asked several critical questions: What are the things associated with better or worse outcomes for patients? Are there different outcomes by geographic region? And lastly, what's it all costing and will it be sustainable?

Researchers looked at a number of variables, from how fast test results were recorded to how patients fared when nurses rather than doctors prescribed drugs. Now, after several clinical trials and an analysis of a vast quantity of data, Botswana has some answers.

Report Card

"What we showed with the Models of Care project is that the national ART program is doing well," said Marlink. "Consistently, the program is improving year by year. The mortality rates are going down. Overall, I'd give it a grade of an A or A-.

Specifically, research showed that as the life of the program increased, the odds of patients' survival improved. When looking at costs, the team projected that the cost of treatment per patient would reach $430 USD in 2014, compared to $357 in 2011. The total cost of the program is projected to reach $99 million in 2014 when patient enrollment is estimated to be just over 200,000. The primary costs for providing ARTs are the drug themselves, laboratory tests, and personnel.

Researchers were not surprised to discover that overall the national program was doing well. What surprised them was finding a huge difference in mortality rates between different locations. "Some districts have a very low mortality rate and some districts have a very high rate," said Dr. Mansour Farahani, a research scientist at HAI. "Statistically controlling for everything, you have a wide variation." Or, as Marlink explained, "to put it bluntly, if you're in the treatment program, you're much more likely to die in one location versus another."

Even with a thorough analysis of the data, researchers could not explain the difference in mortality. Some urban hospitals did well, while others lagged far behind. The same was true for rural clinics. "All the worst cases from across the country are referred to Princess Marina Hospital in Gaborone, so you'd expect to see the worst scenario there," said Farahani. "But they have the best scenario."

Next Steps

The next challenge is to figure out why the large difference in mortality exists between districts. "Why are things going so well in some places and not so well in other places?" asks Marlink. Why would brothers with similar genetics and a similar disease progression have such different outcomes depending on where they live?

"We think there are contextual factors, not just how the clinic is structured," said Marlink. "What is the community like? What are the socio-economic factors? What are other disease burdens?"

"It is a very complicated picture," said Farahani, an expert in improving the effectiveness of health care programs. "We can't say this is because they don't have a lab close by, or enough supplies, or enough nurses, or enough training. It's a combination of things." He is designing a new study to determine which factors are most important for improving health outcomes.

If HAI researchers can figure out how to improve AIDS treatment on a national scale, their work will have far-reaching consequences, both for the two brothers from Botswana, but also for the millions of men and women currently on ART in Africa. In order to sustain large treatment programs, it's essential to find the most efficient and cost-effective way to do so.

"If we get more information about the districts and what's associated with better outcomes, then we can say this model for this type of district seems to work best," said Marlink. "You have to know what's actually happening before you can bring the worst up to the level of the best."

Models of Care was a joint project with the Botswana Ministry of Health and the Botswana-Harvard Partnership and was funded by the African Comprehensive HIV/AIDS Partnerships (ACHAP).
Essex Honored

On May 19th, Max Essex, Chair of HAI, received an honorary Doctorate of Sciences from Haverford College for his work as a “pioneer in building our epidemiological understanding of AIDS, for his groundbreaking research on the nature and transmission of HIV/AIDS, and for his tireless work around the globe to limit the spread of the disease, which has saved countless lives and will save countless more.”

AIDS Care on a Grand Scale

The introduction of antiretroviral therapy (ART) in the 1990s meant that AIDS was no longer an automatic death sentence, at least in the U.S. and Europe. Because of high costs and logistical concerns, there was skepticism about whether large ART programs would work in Africa. In 2001, Botswana’s leaders made a commitment to provide ARTs to all eligible citizens. With help from the Harvard AIDS Initiative and others, they built a national program from the ground up. In this issue of Spotlight, you’ll read about the challenges of turning that ambitious goal into a reality.