A DECADE AGO, WHEN THE WEALTHY COUNTRIES OF THE WORLD reached into their pockets to help the less fortunate combat HIV/AIDS, they came up with a mere $485 million. Last year, the HIV war chest for these developing countries, including some money from their own budgets, totaled $10 billion, more than a 20-fold increase.

A variety of factors contributed to this extraordinary surge in funding, but one stands out: success with anti-HIV drugs. Drugs made little headway against the virus in the decade following the proof in 1984 that HIV causes AIDS. But in 1994, a study showed that AZT could prevent transmission from an HIV-infected pregnant woman to her baby. Then in late 1995, researchers reported that potent anti-HIV drugs used in combination could stave off AIDS and improve the health of those already sick. By the late 1990s, studies in Thailand and Uganda had shown cheaper, simpler ways to prevent mother-to-child transmission (MTCT) with anti-HIV drugs, and Brazil and Haiti demonstrated that if the will existed, treatment could reach rich and poor alike. But for tens of millions of people, that wasn’t happening.

At the 2000 international AIDS conference in Durban, South Africa, the issue of “universal access” came to a full boil, and the next year, the United Nations General Assembly held a special session on HIV/AIDS, sparking a global effort to increase access to, and reduce the costs of, anti-HIV drugs. Billions of new dollars from new sources began flowing into poor countries. First came the World Bank’s Multi-Country HIV/AIDS Program (MAP) in 2000 that spread grants and loans with generous terms to many hard-hit spots. In 2002, the Global Fund to Fight AIDS, Tuberculosis, and Malaria—a partnership of governments, philanthropies, civil society, industry, and affected communities—opened its doors to all comers and, in a novel twist, asked governments to detail their needs and linked payments to performance. U.S. President George W. Bush the next year launched the President’s Emergency Plan for AIDS Relief (PEPFAR).

The Great Funding Surge

HIV/AIDS now attracts billions of dollars each year, extending millions of lives. But many remain untreated and, without better prevention, the money will soon fall short.
which quickly ramped up treatment and prevention efforts in 15 “focus” countries. The Bill and Melinda Gates Foundation made HIV/AIDS a priority, investing nearly $2 billion in treatment, prevention, and research to help the poor. In 2006, the General Assembly upped the ante and declared that every HIV-infected person in need of treatment should receive it by 2010. The response “has transformed … how the developed world partners with the developing world in addressing a catastrophic health crisis,” says Anthony Fauci, an architect of PEPFAR and head of the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

HIV-infected people around the globe are now living longer, and several communities have even seen their epidemics start to wane. “Seven years ago, there wasn’t a single African on treatment from a donor program in a global pandemic of unprecedented proportion,” says Jeffrey Sachs, a health economist at Columbia University who in 2000 called the underfunding of AIDS “perhaps the most shocking feature of our generation.” Today, Sachs has toned down his chiding of the wealthy world and even applauds some of its actions. “Now there’s finally a process in place and a glimmering that the epidemic is peaking. Incidence is coming down in some places, treatment is steadily increasing, and health care systems are beginning to rise from nothing.”

But serious problems remain. Many countries, short on health care workers and infrastructure, have had difficulty building prevention and treatment programs. Several “donor darlings” have received the lion’s share of aid money, while some politically troubled countries have received scant help. The Global Fund has suspended or canceled grants because of corruption. Current funding levels won’t come close to providing universal access by 2010, and high rates of new infections—an indication that prevention programs are having limited success—are placing an ever-increasing demand on treatment programs. The vaccine search, the best hope for slowing HIV’s spread, has failed so miserably that leaders in the field recently persuaded Fauci to shift millions slated for clinical trials to more fundamental studies. Several microbicides (topical gels to prevent transmission) similarly have proven
worthless—or even harmful—in large, expensive human studies. In addition, serious questions have emerged about whether all this new money for HIV/AIDS has come at the expense of meeting other pressing health needs.

During the past 6 months, Science has examined how the dollars are being distributed and spent. Which countries, institutions, and researchers have received the largest slices of the pie (see p. 520)? Who has been left out? Which efforts have gotten the most bang for the buck (see p. 518)? What happens when corruption surfaces (see p. 522)? What lessons can governments, clinicians, and communities learn from the smart investments, missed opportunities, and outright mistakes made by other countries (see p. 526)? And how sustainable is the massive treatment rollout now under way?

Hard answers remain elusive, but a few common themes have emerged. Money alone does not solve every problem, but it sure helps. Unfortunately, no master logic matches the distribution of aid to those most in need. Money can do good only if it’s spent in the right ways, and many agree that prevention, in particular, has been shortchanged. For each person who starts treatment, nearly three people become infected, according to recent estimates. “This is not something where you can say, ‘Okay, I fixed it,’ and walk away,” cautions Fauci. “You have to make a long-term commitment with a lot of resources, and it will only be successful if you can bring down the infection rate to a dramatically lower level than it is now. It’s a phenomenal challenge.”

**Fair share?**
The Global Fund, PEPFAR, the World Bank, and the Gates Foundation have contributed the bulk of the funds to help countries cope with HIV/AIDS. An analysis by Science combined all the money contributed since 1989 by these four sources to the 29 countries with the most HIV-infected people. (The analysis omits China, India, Russia, and Indonesia because they have large populations and relatively low HIV prevalences, which means that their prevention and treatment needs differ markedly from those of the other countries.) In committed funds, the 15 PEPFAR focus countries—which account for about half of the HIV-infected people in the world—have received more than 80%. Ethiopia, a PEPFAR country that reports a relatively low HIV prevalence of 2.1%, has more committed money than any other country. Looking at disbursed dollars per HIV-infected person puts the disparities in
a harsher light still. Rwanda, a PEPFAR country, has received $2015 per infected person. Disbursed funds to the Democratic Republic of the Congo (DRC), the Central African Republic, Myanmar (formerly Burma), Sudan, and Zimbabwe amounted to less than $150 per infected person; these five countries together have 3.7 million infected people—more than 10% of the global total.

The universal-access ethos contends that everyone, everywhere should benefit equally from anti-HIV drugs, and the funding surge has ended the era in which the rich had access and the poor did not. But the billions of new dollars have created a new division of haves and have-nots within the developing world. “This large imbalance exists,” says epidemiologist Robert “Robin” Ryder of the University of California, San Diego, who co runs the Central African portion of the U.S. National Institutes of Health–funded International Epidemiologic Database to Evaluate AIDS. As Ryder points out, six of the top 10 recipients of disbursed Global Fund money are also PEPFAR focus countries. “The rich get richer and the poor get poorer,” he says.

Donors have sound reasons for offering little aid to some countries that have large HIV/AIDS epidemics: Corrupt governments, civil wars, and the absence of infrastructure increase the likelihood that money will be wasted. And many of the most fragile states have shaky relations with the biggest donors, including the United States, Europe, Japan, and Australia. “Foreign aid is an extension of foreign policy,” says Peter Piot, head of the Joint United Nations Programme on HIV/AIDS (UNAIDS). “It’s an illusion that it’s based on objective criteria. That’s why I’m a big supporter of the Global Fund. It’s far less influenced than others.”

But unstable countries also have a distinct disadvantage with the Global Fund, Piot concedes, as they are less likely to be able to submit strong proposals. “We’re actually funding to the maximal level that the country is asking and the level in which it can bring evidence that it can make the money work,” says Michel Kazatchkine, head of the Global Fund. “And of course the weaker the country, the greater the gap will be between demand and need.” Kazatchkine adds that the best funded countries continue to struggle, too: “Even in the countries that are darlings of Global Fund and PEPFAR and Gates, … these amounts of money are below the actual need.”

Stefano Bertozzi, a health economist at the National Institute of Public Health in Mexico City, says the distribution of money is more rational today than in the past, but he argues that the “funding orphans” deserve serious attention. “We need to make sure countries in greatest need have access to the funds,” he says. To this end, Aids2span, a Global Fund watchdog based in Nairobi, proposed in an April report that a mentoring program of independent consultants be set up to help countries conceptualize but not write their proposals. “The Global Fund has no mechanism for saying publicly or privately, ‘The gap is huge in country X and small in country Y: What can we do to get more money to country X?’” explains Bernard Rivers, who heads Aids2span (see sidebar, p. 524). “They’re very hands-off. They can’t say, ‘Help us to help you to write a great proposal so we can get you a lot of money.’”

Measuring impact
Donors and researchers have tried to assess the impact of the funding surge and disentangle the overlapping investments. A few clear success stories have emerged, such as prevention of MTCT and reduction of deaths in Botswana. But hard data about reduction in new infections from sexual transmission, and direct evidence that mortality and morbidity have dropped on a country level because of anti-HIV drugs, are the exception to the rule.

PEPFAR and the Global Fund regularly report results of their investments, and the World Bank does periodic assessments. The Gates Foundation, a private philanthropy that does not have to answer to constituents, offers little information about the impact of its programs.

As of June 2008, PEPFAR says it has prevented 7 million infections,
trained some half-million care providers, and “supported” the anti-retroviral (ARV) treatment of 2 million HIV-infected people and the care of 10 million others. The word “support” underscores that PEPFAR often cannot separate its contributions from those made by the Global Fund and domestic spending.

The same month, the Global Fund reported that it had provided anti-HIV drugs to 1.75 million people, helped 2.8 million orphans, provided counseling and testing to 46 million people, and trained 7.6 million people to provide care for HIV/AIDS, TB, and malaria in 136 countries. The World Bank has calculated that 40% of its MAP funds in Africa have gone to “strengthening systems,” which includes everything from training staff of nongovernmental organizations (NGOs) to building infrastructure to improving the supply chain of drugs and testing kits. About one-third of the bank’s money went to prevention efforts, “contributing” to the enrollment of some 1.5 million HIV-infected pregnant women in programs to thwart transmission to their babies. Only 16% of bank funds supported care and treatment, accounting for a modest 27,000 people on anti-HIV drugs by the end of 2005.

Last year’s annual UNAIDS update illustrates the difficulty of determining on a country level the impact of funding. Kenya, which has received ample support from PEPFAR and the Global Fund, had sharp drops in prevalence that appeared in part related to changes in behavior. But so did Zimbabwe, which is not a PEPFAR focus country, has received relatively little from the Global Fund, and, all told, has taken in one-seventh as much aid per infected person as Kenya. Roeland Monasch, a UNICEF representative in Zimbabwe who helped that country prepare a successful Global Fund proposal, says one of the factors accounting for the drop may be the economic crisis. “There’s much less mobility of people in the country, and men can’t afford girlfriends and to travel up to the country in the weekend,” says Monasch.

Ryder contends that the skewed funding to the darlings also undermines attempts to assess the effectiveness of ARV treatment in lowering mortality rates. He notes that PEPFAR focus countries such as Rwanda have the resources to track people who are on anti-HIV treatment, whereas poorer countries such as the DRC don’t. “It really affects assumptions about efficacy,” says Ryder. Say researchers in Rwanda discover that a woman on treatment died from AIDS, whereas if that same woman lived in the DRC, she might be “lost to follow-up” and excluded in the final analysis. “It’s paradoxical,” says Ryder. “The more money you put into a country, the more likely you are to show a higher death rate because you have the wherewithal to know someone died.”

**Strengths and weaknesses**

The “big three” publicly funded HIV/AIDS efforts—the Global Fund, PEPFAR, and the World Bank’s MAP—have all received intense scrutiny—but PEPFAR has attracted by far the most, in part, says Bertozzi, because of initial skepticism about an ambitious new program created by Bush, who many thought had shown little interest in the HIV/AIDS epidemic.

PEPFAR has won over many doubters because of the speed with which it delivers treatment and prevention. Yet some of PEPFAR’s policies have dismayed researchers and HIV/AIDS advocates, who contend that they promote Bush’s religious and political agendas while disregarding scientific evidence on which interventions work best. In particular, critics have assailed PEPFAR for emphasizing abstinence-only education, which they say does little good, and requiring recipients to sign a pledge against prostitution that they say...
further stigmatizes sex workers and discourages prevention outreach efforts geared toward them.

Another concern is that PEPFAR funnels much of its aid through international NGOs—big winners are the U.S.-based Family Health International and Management Sciences for Health—instead of trying to strengthen in-country capacity. In an April 2008 report, epidemiologist Nandini Oomman and colleagues at the Center for Global Development, an independent think tank in Washington, D.C., noted that about 70% of PEPFAR funds have gone to international organizations, many of them faith-based. Says Oomman, “If you’re thinking about a sustainable long-term response, you really do have to think about how you develop local capacity.”

PEPFAR’s head, Mark Dybul, concedes that some investments are skewed to international NGOs, but he says that’s what an effective emergency response requires. “You don’t respond to a tsunami by just sending money to a country and hoping that they take care of all the problems,” says Dybul. And he says that in countries like Uganda that have “more mature” epidemics, this skewing doesn’t occur because they have had time to develop their local response. “It takes a while to build capacity,” Dybul says.

As Science went to press, Congress was expected to reauthorize PEPFAR for the next 5 years, tripling its budget and doing away with some of the most restrictive requirements. The draft law also calls for training and retaining 140,000 new health care workers. Dybul says PEPFAR may decide to make substantial investments beyond the original 15 focus countries.

In contrast to PEPFAR, the Global Fund is more hands-off, seeing itself as little more than a financing mechanism. “Our funding is based on a fundamental principle: country ownership,” says director Kazatchkine. Yet some contend that the fund would have more impact if it had people in countries who helped, as PEPFAR and the World Bank do.

Country ownership sometimes trades autonomy for economy. Consider the purchase of drugs, which Global Fund recipients negotiate independently. Epidemiologist Brenda Waning of Boston University School of Public Health says there is a “ridiculous” variability in how much different Global Fund recipients pay for anti-HIV drugs. “Some countries are paying 15 times as much as other countries,” says Waning. “The Global Fund, from what I can tell, doesn’t seem as though they bother looking at prices people are paying.”

The World Bank’s MAP program, too, has struggled to conduct proper evaluation and monitoring and has created overly cumbersome procedures to disburse money, according to two in-depth analyses published by the bank in 2005. These sharply self-critical reports described the impact of the bank-sponsored projects as “uneven” and also faulted MAP for “grossly” neglecting research to evaluate the cost-effectiveness of different interventions.

The big three are all still fairly young, and the introspection and outside criticism continues to push each one to improve. But health economist Bertozzi says more attention should be paid to how they fit together. “It’s a shame that there’s no demand to look at the relative strengths and weaknesses and efficiencies of funding HIV programs through three different models,” says Bertozzi. “Probably the most efficient way to spend the money is some mix of those three.”

Never-ending

Even if they differ on which funding mechanism works best, experts
HIV/AIDS: Follow the Money

Bang for the Buck

Three modest NIH investments yield big dividends

Much of the nearly $3 billion the U.S. National Institutes of Health (NIH) spends on HIV/AIDS research each year supports basic studies that may not yield insights for decades. But three relatively modest investments continue to advance the field in ways large and small, year after year. Together, they consume about $20 million a year—not even 1% of the entire budget—and help thousands of researchers around the world at no cost. “I think of these three as the gifts that keep on giving,” says Anthony Fauci, head of NIH’s National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, which funds these projects.

NIH AIDS Research and Reference Reagent Program
Annual budget: $3.75 million
Location: Germantown, Maryland

Say you’re running an experiment that calls for some HIV in the flavor known as subtype C. Or maybe it’s a dash of the protease inhibitor indinavir, a dollop of a monoclonal version of the b12 antibody, or a sprinkle of the human version of the APOBEC3B protein. Each of these reagents is yours, free, aside from a nominal shipping fee.

Since 1988, the NIH AIDS Research and Reference Reagent Program has asked investigators to share interesting samples of HIVs, antibodies, peptides, antivirals, cell lines, proteins, and expression vectors. A nondescript office building in an aging business park now warehouses 8500 unique reagents. Last year, the program sent out 15,800 small samples of reagents to nearly 4000 scientists in 65 countries, often within a week.

Opendra Sharma of NIAID, who runs the program, says researchers typically are “very happy” to supply samples as long as recipients agree not to use them for commercial purposes. And when Sharma and his team run across someone who does not want to share, they have their methods of persuasion, he says: “We twist their arms, but we don’t break them.”

A recent survey of nearly 800 users showed 98% or higher satisfaction. But 10% complained that they did not receive enough reagents in high enough quantities. As a rule of thumb, investigators are allowed two samples per grant per year, though Sharma says they make exceptions.

Multicenter AIDS Cohort Study
Annual budget: $14.4 million
Location: Chicago, Los Angeles, Baltimore, Pittsburgh

How long does it take to progress from HIV infection to symptomatic disease? What percentage of people live with HIV for more than a dozen years and suffer no harm? Why do some people remain invulnerable to HIV, despite repeated exposure? These are a few of the questions that researchers have probed, thanks to blood samples collected during nearly 25 years by the Multicenter AIDS Cohort Study (MACS). This unusual study has followed thousands of people at high risk of becoming infected with HIV or developing AIDS.

When MACS began in 1984, researchers had yet to prove that HIV causes AIDS. The study at first recruited 5622 gay and bisexual men in four U.S. cities, and each agreed to provide a blood sample and personal history every 6 months. When an HIV antibody test became available the next year, the researchers realized that half the men were infected at the study’s start. “The real

agree on one thing: The massive influx of dollars is not keeping up with the pace of the HIV/AIDS epidemic.

In an article in the February 2008 issue of AIDS, researchers reported that Uganda, a PEPFAR country and one of the top aid recipients, expects to more than double the number of people receiving anti-HIV drugs between 2005 and 2010. Given the country’s projected population growth, however, the number of people who need treatment but aren’t receiving it will hardly decline. “It’s hard to imagine, at least with the way we’re currently doing things, that we can achieve universal access by 2010,” says co-author John Stover, a public health analyst who heads the Futures Institute in Glastonbury, Connecticut. “Not only is the number newly in need increasing each year, you need to continue the people on treatment who are surviving.” The study bluntly concludes: “Although current prevention and treatment programmes have a measurable effect on the burden of disease, they may not substantially alter the face of the epidemic in the near future.”

Using global projections from Stover and others, UNAIDS projects that if prevention and treatment scale-up continues at the same pace as today, by 2010, it will cost $42.2 billion—more than four times the amount available today—to reach 80% (13.7 million people) of those who will then be in need. As of the end of 2007, UNAIDS said 3 million were receiving treatment in low- and middle-income countries, which is about 30% of those who need it.

The only way out of this dilemma, assert Stover, UNAIDS’s Piot, and many others, is to invest more in proven prevention interventions and tailor the response to each country’s epidemic. “The critical question is not just how much money is available [for prevention], but how much is being spent in the right ways,” says epidemiologist Elizabeth Pisani, author of the Wisdom of Whores, published earlier this year.

One problem, says Pisani, who previously worked for Family Health International in Indonesia, is the misconception that HIV/AIDS is one epidemic, when in fact it is two: One is in sub-Saharan Africa, where several countries have “generalized” prevalences above 2%; the other is the “concentrated” epidemic in the rest of the world that occurs mainly in high-risk groups such as men who have sex with men (MSM), injecting drug users, and sex workers. For generalized epidemics, everyone above the age of 13 is at risk, she says, and prevention efforts should have a broad agenda. But for concentrated epidemics, it makes more sense to focus on the high-risk groups.

Far too often, says José Antonio Izazola-Licea, who heads the financing and economic division of UNAIDS, countries with concentrated epidemics don’t focus their efforts on their high-risk groups. Similarly, says Stover, many countries disproportionately spend prevention money on MTCT even when they have low infection rates and low birth rates. Ten leading AIDS researchers recently argued that not enough effort has gone into promoting male circumcision and the importance of reducing multiple partners (Science, 9 May, p. 749).

Prevention efforts directed at high-risk groups can have a major impact in generalized epidemics, too, says epidemiologist Prabhath Jha of the University of Toronto in Canada. In a meta-analysis of 68 epidemiologic studies from Africa in the October 2007 issue of PLoS One, Jha and colleagues found that “superspreaders” accounted for a disproportionate
strength of the MACS is we had these men who had the same lifestyle but were uninfected,” says John Phair of Northwestern University in Chicago, Illinois, who chairs the MACS executive committee. Basically, the researchers had a built-in control group that enabled them to tease out just how HIV causes AIDS.

Today, 150 MACS investigators follow about 3000 men: Roughly 1600 are infected, and nearly 90% of those are taking anti-HIV drugs. Over the course of the study, investigators have stored more than 1 million samples of plasma, serum, and cells. Culled data, made publicly available, include more than 100,000 entries of CD4 counts—the white blood cells that HIV progressively destroys—and tens of thousands of measurements of the amount of virus in individuals at different times. “The participants give a lot of blood,” says Phair. “They’re very generous.”

The HIV Databases
Annual budget: $1.95 million
Location: Los Alamos National Laboratory, New Mexico

Working on GenBank, the genetic sequence database at Los Alamos, Gerald Myers in 1986 became fascinated by the genetic differences between HIV variants. He soon emerged as a world expert on HIV genetic diversity, building a public database that has helped researchers trace the origin of the epidemic, design vaccines, understand viral evolution, track drug-resistance mutations, and even investigate possible skull-duggery between competing AIDS researchers.

Myers handed off the project more than a decade ago to immunologist Bette Korber, who added an immunology database that offers some of the most detailed, comprehensive information available about how the virus interacts with immune cells. The immunology database can also interact with what are now almost 250,000 HIV sequences in the older database. Yet another database lets researchers peruse results of all known AIDS vaccine studies done in nonhuman primates. “It’s not the quantity of the data but the quality that make the databases stand out,” says Korber.

And that quality keeps the quantity of Web site hits high: Last year, the total came to 1.5 million unique visits.

—J.C.

amount of transmission even in high-prevalence countries. “The role of superspreaders is still very central to the African epidemic,” says Jha.

Epidemiologist Sharon Weir of the University of North Carolina, Chapel Hill, suggests that one way to find superspreaders is to identify where sexual transactions occur—such as truck stops, bars, and street corners—and provide prevention interventions there. People in high-risk groups, notes Weir, often don’t identify themselves as MSM or sex workers.

Techniques to identify the newly infected could also slow HIV’s spread. In some studies, nearly half of the people who became infected had partners who had recently become infected themselves. These highly infectious people in the acute stage of the disease often have yet to develop antibodies against HIV, but tests exist that can pluck out viral genetic material from blood. In 2005, researchers described how they used a relatively inexpensive technique to identify acutely infected people who gave blood at HIV testing sites (Science, 12 August 2005, p. 1002). Basically, they cut costs by removing a small amount of blood from individual vials and pooling them. If a pool tests positive for HIV RNA, they could backtrack and find the acutely infected people, who were then contacted and counseled. Principal investigator Christopher Pilcher of the University of California, San Francisco, is now testing the approach in Brazil, and other groups are trying it in Malawi, Tanzania, and South Africa. Detecting acute infection will be a major prevention strategy, Pilcher says, but cautions that their test is still technically difficult in most developing countries: “The truth is very, very few people are working on this because it has not been identified as a priority.”

Displacement?

Amid all the back and forth about how best to provide treatment and prevent HIV transmission, some analysts are arguing that maybe the disease receives proportionally more money than it merits.

In a paper in the 21 December issue of Health Policy and Planning, Jeremy Shiffman, a political scientist at Syracuse University in New York, compared donor funding for HIV/AIDS from 1992 to 2005 with money spent on infectious disease, health sector development, and population control. Shiffman found declines in the latter two, leading him to ask whether HIV/AIDS had “displaced” these important public health issues. Shiffman emphasizes that he believes HIV/AIDS doesn’t receive enough funding. But he thinks global health equity matters, too, “Do we really want a situation where if you have AIDS you get treated and if you’re a baby with pneumonia you die? Wouldn’t we rather have a health system for both folks?”

Stover of the Futures Institute questions the displacement idea, arguing that money for HIV/AIDS may well be strengthening health systems across the board. He also doesn’t rule out the possibility that the wealthy world may devote even more to HIV/AIDS. As Stover sees it, “I’d hate to say, ‘No way.’ If you asked me 5 years ago whether we’d get to 3 million on treatment, I would have scoffed. One of the things Jeff Sachs has taught us all is because we haven’t been able to get that amount of money in the past, it doesn’t mean we won’t be able to get it in the future.”

—JON COHEN