



DISEASE CONTROL  
PRIORITIES PROJECT



# HIV & TB

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# Contents

1	Tuberculosis .....	1
	<i>Disease Control Priorities in Developing Countries</i>	
	Christopher Dye and Katherine Floyd	
2	HIV/AIDS Prevention and Treatment .....	25
	<i>Disease Control Priorities in Developing Countries</i>	
	Stefano Bertozzi, Nancy S. Padian, Jeny Wegbreit, Lisa M. DeMaria, Becca Feldman, Helene Gayle, Julian Gold, Robert Grant, and Michael T. Isbell	

Part **Two**

## Selecting Interventions

- Infectious Disease, Reproductive Health, and Undernutrition
- Noncommunicable Disease and Injury
- Risk Factors
- Consequences of Disease and Injury



## Chapter 16

# Tuberculosis



Christopher Dye and Katherine Floyd

Despite the availability of drugs to cure tuberculosis (TB) since the 1940s, TB remains an important cause of death from an infectious agent, second only to the human immunodeficiency virus, or HIV (WHO 2004f). TB control is high on the international public health agenda, not only because of the enormous burden of disease, but also because short-course chemotherapy (SCC) is recognized as one of the most cost-effective of all health interventions (Jamison and others 1993). That recognition is partly attributable to an influential series of studies done in three of the poorest countries of southeastern Africa (Malawi, Mozambique, and Tanzania), which suggested that a year of healthy life could be gained for less than about US\$5 (de Jonghe and others 1994; Murray and others 1991). This evidence has been central to the global promotion of the DOTS strategy, the package of measures combining best practices in the diagnosis and treatment of patients with active TB, in which direct observation of treatment during SCC is a key element (WHO 2002a, 2004c).

Although the World Health Organization (WHO) has fostered the implementation of DOTS over the past decade, four recent developments have drawn attention to a wider range of options for TB control:

- First, many more studies have investigated the costs, efficacy, and cost-effectiveness of different approaches to TB control. They are mostly studies of ways to improve the delivery of first-line drug treatment for active disease, but they include some investigations of preventive therapy (treatment of latent infection), treatment of multidrug-resistant TB (MDR-TB) using both first- and second-line drugs, and different approaches to diagnosis. They have been carried out in a variety of settings, in richer as well as poorer coun-

tries. The results have not been fully synthesized but may suggest ways to enhance DOTS.

- Second, striking increases in TB have been associated with the spread of HIV infection and drug resistance, suggesting that DOTS alone may not be enough to bring TB under control, especially in Africa and in the countries of the former Soviet Union.
- Third, there is now substantially more investment in new tools for TB control, including multimillion-dollar initiatives to develop better diagnostics, drugs, and vaccines, many of which operate under the umbrella of the Stop TB Partnership (see <http://www.stoptb.org>). Some of the possible products of this new research would stimulate reevaluations of the current reliance on chemotherapy, especially the development of a new high-efficacy vaccine.
- Fourth, interest in TB is renascent, not simply as the outcome of mycobacterial infection, but also as the consequence of exposure to exacerbating risks, such as tobacco smoke, air pollution, malnutrition, overcrowding, and poor access to health services. Research directed at quantifying these risks will also suggest ways to minimize them.

These developments set a big agenda for analysis. To make some inroads, this chapter presents an overview of the value for money and potential effect of the principal modes of TB control around the world. The starting point is a review of the natural history and clinical characteristics of TB and the geographical distribution of and trends in TB cases and deaths. This introduction sets the context for a discussion of the interventions that are now available to control TB and of how they have been used. We use a new method for evaluating the cost-effectiveness of infectious disease control and apply

this method systematically to four groups of TB interventions as they could be implemented in six regions of the world.

The internationally agreed-on targets for TB control, embraced by the United Nations Millennium Development Goals (MDGs), are to detect 70 percent of sputum-smear-positive cases and successfully treat 85 percent of such cases by the end of 2005. The expectation is that, if these targets can be reached and maintained, incidence rates will be falling by 2015, and the TB prevalence and death rates of 1990 will be halved by 2015. Meeting these targets requires a set of interventions that are not only cost-effective but also affordable and capable of having an effect on a large scale. The final sections of the chapter discuss the absolute costs and benefits of global TB control and the potential for achieving the effect defined within the MDG framework. The main themes of the text that follows are elaborated in a series of annexes available online at <http://www.fic.nih.gov/dcpp> as well as at <http://www.who.int/tb/publications/en/>.

## TUBERCULOSIS INFECTION, DISEASE, AND DEATH

Human TB is caused by infection with mycobacteria, principally *Mycobacterium tuberculosis*. Individuals with pulmonary or laryngeal TB produce airborne droplets while coughing, sneezing, or simply talking. Inhaled infectious droplets lodge in the alveoli, and bacilli are taken up there by macrophages, beginning a series of events that results in either the containment of infection or the progression to active disease (Frieden and others 2003). Following uptake by macrophages, *M. tuberculosis* replicates slowly but continuously and spreads through the lymphatic system to hilar lymph nodes. In most infected people, cell-mediated immunity, associated with a positive tuberculin test, develops two to eight weeks after infection. Activated T lymphocytes and macrophages form granulomas, which limit the further replication and spread of bacilli. Unless a later defect occurs in cell-mediated immunity, the infection remains contained within the granulomas.

The immune mechanisms are, in their details, far more complex. For example, following antigenic challenge, a suite of different T cells is responsible for the induction and suppression of protective immunity, delayed hypersensitivity, cytolysis, and the production of antibodies and memory cells. Helper T cells mature into two functionally different populations: in *M. tuberculosis* infection, the  $T_H1$  response is associated with granuloma formation and protection, whereas the  $T_H2$  response results in tissue-necrotizing hypersensitivity and the progression of disease. The processes that determine the balance of the two responses affect, for example, the interaction between *M. tuberculosis* and other infectious agents (Grange 2003).

When the immune response cannot suppress replication, primary infection leads to active TB (progressive primary TB).

The most common clinical manifestation is pulmonary disease, typically in the parenchyma of the middle and lower lung. In the most infectious patients, bacilli can be seen microscopically on stained sputum smears (60 to 70 percent of pulmonary cases; Marais and others 2004; Styblo 1991). Smear-negative patients may also be infectious but, per patient, contribute relatively little to transmission (Behr and others 1999; Hernandez-Garduno and others 2004). Extrapulmonary tuberculosis accounts for 10 to 30 percent of the disease but is more common among women and children (particularly lymphatic TB) and in people infected with HIV (Aaron and others 2004; Rieder 1999; Rieder, Snider, and Cauthen 1990; Shafer and Edlin 1996).

In the absence of other predisposing conditions, only about 5 percent of infected people develop progressive primary disease within five years of infection (Comstock, Livesay, and Woolpert 1974; Sutherland 1968, 1976). After five years, the annual risk of developing TB by the reactivation of latent infection is much lower ( $\approx 10^{-4}$  per capita per year). The risk of progressing to active disease is relatively high in infancy and lower in older children; it increases quickly during adolescence (earlier in girls) and then more slowly throughout adulthood (Comstock, Livesay, and Woolpert 1974; Nelson and Wells 2004; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997). Whether latent bacilli remain viable for the full life span of all infected people is unknown, but the risk of reactivation certainly persists into old age. The lifetime risk of developing TB following infection clearly depends on the prevailing transmission rate; the rule of thumb is 10 percent, but it has been calculated at 12 percent for all forms of pulmonary disease in England and Wales during the second half of the 20th century (Vynnycky and Fine 2000).

Besides the strong innate resistance to developing disease, infection is associated with an acquired immune response. This response is only partially protective (Dye and others 1998; Sutherland, Svandova, and Radhakrishna 1982; Vynnycky and Fine 1997), which helps explain why developing an effective vaccine has been difficult (few manufactured vaccines are more protective than natural immunity; Andersen 2001; Fordham von Reyn and Vuola 2002; Young and Stewart 2002). Consequently, individuals who carry a latent infection and who continue to be exposed are at risk of TB following reinfection. The importance of reinfection remains controversial, but mathematical modeling shows that the decline of TB in Europe cannot easily be explained without reinfection (Dye and others 1998; Vynnycky and Fine 1997). In addition, molecular fingerprinting has produced direct evidence that TB commonly arises from infection and reinfection in endemic areas (de Viedma and others 2002; Richardson and others 2002; van Rie and others 1999; Verver and others 2004), especially where subjects are infected with HIV (Glynn and others 2004).

The low incidence of infection and the low probability of breakdown to disease explain why TB is relatively rare. Its importance among infectious diseases is attributable not so much to the number of cases as to the high case-fatality rate among untreated or improperly treated patients. About two-thirds of untreated smear-positive patients will die within five to eight years, the majority within the first 18 months (Styblo 1991). Most of those who are still alive after eight years will have quiescent TB (self-cures, susceptible to relapse), and a few will become chronic excretors of bacilli. The case-fatality rate for untreated smear-negative cases is lower, but still of the order of 10 to 15 percent (Krebs 1930; Rieder 1999). Even among smear-positive patients receiving antituberculosis drugs, the case-fatality rate can exceed 10 percent if adherence to treatment is low or if rates of HIV infection and drug resistance are high (WHO 2004c).

Online annex 1 contains more information about factors that affect the risk to individuals of contracting infection and developing disease and the distribution of TB in populations.

## EPIDEMIOLOGICAL BURDEN AND TRENDS

Surveys of the prevalence of infection and disease, assessments of the performance of surveillance systems, and death registrations yield an estimated 8.8 million new cases of TB in 2003, fewer than half of which were reported to public health authorities and WHO (online annex 2). Approximately 3.9 million cases were sputum-smear positive, the most infectious form of the disease (Corbett and others 2003; Dye and others 1999; WHO 2005). The African region has the highest estimated incidence rate (345 per 100,000 population annually), but the most populous countries of Asia harbor the largest number of cases: Bangladesh, China, India, Indonesia, and Pakistan together account for half the new cases arising each year. In terms of the total estimated number of new TB cases arising annually, about 80 percent of new cases occur in the top-ranking 22 countries.

In most countries (but not all), more cases of TB are reported among men than women. This differential is partly because women have less access to diagnostic facilities in some settings (Hudelson 1996), but the broader pattern also reflects real epidemiological differences between men and women, both in exposure to infection and in susceptibility to disease (Borgdorff and others 2000; Hamid Salim and others 2004; Radhakrishna, Frieden, and Subramani 2003). Where the transmission of *M. tuberculosis* has been stable or increasing for many years, the incidence rate is highest among young adults, and most cases are caused by recent infection or reinfection. As transmission falls, the caseload shifts to older age groups, and a higher proportion of cases comes from the reactivation of latent infection.

Globally, the TB incidence rate per capita appears to be growing slowly (online annex 2). Case numbers have been declining more or less steadily for at least two decades in Western and Central Europe, the Americas, and the Middle East. Striking increases have occurred in countries of Eastern Europe (mainly the former Soviet republics) since 1990 and in Sub-Saharan Africa since the mid 1980s, although trends in case notifications suggest that the rate of increase in both regions has slowed significantly since the mid 1990s (WHO 2005).

TB has increased in Eastern European countries because of economic decline and the general failure of TB control and other health services since 1991 (Shilova and Dye 2001). Periodic surveys indicate that more than 10 percent of new TB cases in Estonia, Latvia, and some parts of the Russian Federation are multidrug-resistant—that is, resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs (Espinal and others 2001; WHO 2004a). Drug resistance is likely to be a by-product of the events that led to TB resurgence in these countries, not the primary cause of it, for three reasons. First, resistance is generated initially by inadequate treatment caused, for example, by interruption of the treatment schedule or use of low-quality drugs. Second, resistance tends to build up over many years, and yet TB incidence increased suddenly in Eastern European countries after 1991. Third, although formal calculations have not been done, resistance rates are probably too low to attribute all of the increase in caseload to excess transmission from treatment failures.

Globally, 12 percent of new adult TB cases were infected with HIV in 2003, but there was marked variation among regions—from an estimated 33 percent in Sub-Saharan Africa to 2 percent in East Asia and the Pacific (online annex 2). HIV infection rates in TB patients have so far remained below 1 percent in Bangladesh, China, and Indonesia. The increase in TB incidence in Africa is strongly associated with the prevalence of HIV infection (Corbett and others 2002), and in populations with higher rates of HIV infection, women 15–24 years old constitute a higher proportion of TB patients (Corbett and others 2002). The rise in the number of TB cases in Africa is slowing, almost certainly because HIV infection rates are also beginning to stabilize or fall (Asamoah-Odei, Garcia Calleja, and Boerma 2004). HIV has probably had a smaller effect on TB prevalence than on incidence because HIV significantly reduces the life expectancy of TB patients (Corbett and others 2004). Where HIV infection rates are high in the general population, they are also high among TB patients; estimates for 2003 suggested that more than 50 percent of TB patients infected with HIV in Botswana, South Africa, Zambia, and Zimbabwe, among other countries.

Approximately 1.7 million people died of TB in 2003 (Corbett and others 2003), including 229,000 patients who were also infected with HIV (online annex 2). Although these

are usually reported as AIDS deaths under the *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10), and by WHO, TB control programs need to know the total number of TB deaths, whatever the underlying cause.

## INTERVENTIONS AGAINST TUBERCULOSIS

TB can be controlled by preventing infection, by stopping progression from infection to active disease, and by treating active disease. The principal intervention is the DOTS strategy and its variations, centered on the diagnosis and treatment of the most severe and most infectious (smear-positive) forms of TB but including treatment for smear-negative and extrapulmonary cases as well. Anti-TB drugs can also be used to treat latent *M. tuberculosis* infection and active TB in patients with HIV coinfection, and the widely used bacillus Calmette-Guérin (BCG) vaccine prevents (mainly) severe forms of TB in childhood. These biomedical interventions directed specifically against TB can be implemented in a variety of ways through medical services and public action and can be supported by other efforts to reduce environmental risk factors (online annex 1).

### Vaccination

Currently, the only means of immunizing against TB is with the live attenuated vaccine BCG, although other vaccines are under development (Fruth and Young 2004; Goonetilleke and others 2003; Horwitz and others 2000; Letvin, Bloom, and Hoffman 2001; Reed and others 2003; Young and Stewart 2002). Randomized controlled trials and case-control studies have shown consistently high protective efficacy of BCG against serious forms of disease in children (73 percent [95 percent confidence limits 67–79 percent] for meningitis and 77 percent [95 percent confidence limits 58–87 percent] for miliary TB) but highly variable—and often very low—efficacy against pulmonary TB in adults (Bourdin Trunz, Fine, and Dye, forthcoming; Fine 2001; Rieder 2003). Thus, even with the high coverage now achieved, BCG is unlikely to have any substantial effect on transmission. In parts of Europe and North America that did and did not use BCG, TB declined at rates that were not measurably different (Styblo 1991). In areas of high incidence, BCG vaccination is recommended for children at birth or at first contact with health services. Vaccination is being discontinued in many low-incidence countries because the risk of infection is low and because the response to BCG confounds the interpretation of tuberculin skin tests used to track persons infected during occasional outbreaks. BCG may have substantial nonspecific effects on child mortality—that is, in reducing deaths from causes other than TB—but this possibility is still controversial (Kristensen, Aaby, and Jensen 2000).

Reported BCG vaccination coverage has increased throughout the world during the past 25 years, reaching about 100 million infants, or 86 percent of all infants, in 2002. An estimated 92 percent of children were vaccinated in Europe and 62 percent in Africa in 2002 (WHO 2001). During the past 15 years, coverage has generally been most variable among African countries and least variable in Europe and the Americas. The most complete analysis of the effect of BCG vaccination suggests that BCG given to children born in 2002 prevents about 29,700 cases of childhood meningitis and 11,500 cases of miliary TB during the first five years of life, or one case for every 3,400 and 9,300 vaccinations, respectively (Bourdin Trunz, Fine, and Dye, forthcoming).

### Treatment of Latent Infection

Individuals at high risk of TB who have a positive tuberculin skin test but not active disease (for example, associates of active cases, especially children and immigrants to low-incidence countries) can be offered treatment for latent TB infection (TLTI), most commonly with the relatively safe and inexpensive drug isoniazid. Studies among those who have contacts with active cases have demonstrated that 12 months of daily isoniazid gives 30 to 100 percent protection against the development of active TB (Cohn and El-Sadr 2000; Comstock 2000). For patients who may be carrying a strain resistant to isoniazid, rifampicin daily for 4 months is an acceptable alternative (or rifabutin, if used with protease inhibitors for HIV-infected people; Cohn 2003; Menzies and others 2004). Nevertheless, TLTI is not widely used. The main reason is that compliance with long-term daily treatment tends to be poor among healthy people—a relatively high risk of TB among those who are latently infected is usually still a low risk in absolute terms. An additional reason is that the tuberculin skin test tends to be less specific when applied to individuals who have been vaccinated with BCG. Although it is sometimes possible to make separate estimates of the number of individuals in a population who have been infected and who have received BCG (Neuenschwander and others 2002), distinguishing the responses to BCG and infection is harder in any given individual.

The exceptionally high risk of TB among persons coinfecting with *M. tuberculosis* and HIV is a reason for encouraging wider use of TLTI, especially in Africa. However, there are significant barriers to making TLTI effective for coinfecting individuals living in areas of high transmission (in addition to those listed earlier). Although trials of TLTI with individuals infected with HIV whose tuberculin skin test was positive have averaged about 60 percent protection for up to three years (with a good deal of variability), the effects have been lost soon afterward, and little or no effect has been seen on mortality (Bucher and others 1999; Johnson and others 2001; Mwinga and others 1998; Quigley and others 2001; Whalen and others 1997; Wilkinson,

Squire, and Garner 1998). In addition, identifying *M. tuberculosis* infection is more difficult in HIV-positive individuals than in those who are HIV-negative because the former are often anergic and are, therefore, unresponsive to tuberculin. Early studies have also experienced problems with uptake and compliance. In a pilot project in Zambia, for example, only 35 percent of HIV-infected individuals identified through HIV testing and counseling services actually started TLTI, and, of those who started, only 23 percent completed at least six months of treatment (Terris-Prestholt and Kumaranayake 2003).

TLTI has been used as a component of intensive, local control campaigns, such as those carried out for North American and Greenland Eskimos, but probably had effects secondary to the prompt treatment of active disease (Comstock, Baum, and Snider 1979; Styblo 1991). At present, TLTI plays no more than an accessory role in TB control in any setting, although the number of recipients around the world has been neither directly quantified nor indirectly estimated.

### **Treatment of Active Disease: The DOTS Strategy**

The cornerstone of TB control is the prompt treatment of active cases with SCC using first-line drugs, administered through the DOTS strategy (WHO 2002a) within targets framed by the MDGs. The DOTS strategy has five elements:

- political commitment
- diagnosis primarily by sputum-smear microscopy among patients attending health facilities
- SCC with effective case management (including direct observation of treatment)
- a regular drug supply
- systematic monitoring to evaluate the outcomes of every patient started on treatment.

Standard SCC can cure more than 90 percent of new, drug-susceptible TB cases, and high cure rates are a prerequisite for expanding case finding. Although the DOTS strategy aims primarily to provide free treatment for smear-positive patients, most DOTS programs also treat smear-negative patients, usually without a fee. DOTS can be used as the basis for more complex TB control strategies where rates of drug resistance or HIV infection are high.

Mathematical modeling and practical experience suggest that the incidence of TB will decline at 5 to 10 percent per year when 70 percent of infectious cases are detected through passive case finding and 85 percent of these cases are cured, even though that level represents a treatment success rate among all infectious cases of only 60 percent (Dye 2000; Dye and others 1998). In principle, TB incidence could be forced down more quickly, by as much as 30 percent per year, if new cases could be

found soon enough to eliminate transmission. In general, the decline will be faster where a larger fraction of cases arises from recent infection (that is, in areas where transmission rates have recently been high) and slower where there is a large backlog of asymptomatic infection. As TB transmission and incidence go down, a higher proportion of cases comes from the reactivation of latent infection and the rate of decline in incidence slows. These facts explain why it should be easier to control epidemic than endemic disease: during an outbreak in an area that previously had little TB, the reservoir of latent infection will be small, and most new cases will come from recent infection.

In the control of endemic TB, largely by chemotherapy, the best results have been achieved in communities of Alaskan, Canadian, and Greenland Eskimos, where incidence was reduced at 13 to 18 percent per year from the early 1950s (Styblo 1991). Over a much wider area in Western Europe, TB declined at 7 to 10 percent per year after drugs became widely available during the 1950s, although incidence was already falling at 4 to 5 percent per year before chemotherapy (Styblo 1991). More recently, between 1994 and 2000, the incidence of pulmonary TB among Moroccan children 0 to 4 years of age fell at more than 10 percent per year, suggesting that the risk of infection was falling at least as quickly (S. Ottmani, personal communication 2005). The overall reduction in pulmonary TB was only 4 percent per year, in part because of the large reservoir of infection in adults. DOTS was launched in Peru in 1991, and high rates of case detection and cure appear to have pushed down the incidence rate of pulmonary TB by 6 percent per year (Suarez and others 2001). For epidemic TB, as a result of aggressive intervention following an outbreak in New York City, the number of MDR-TB cases fell at a rate of more than 40 percent per year (Frieden and others 1995).

Although the long-term aim of TB control is to eliminate all new cases, cutting prevalence and death rates is arguably more important. About 86 percent of the burden of TB, as measured in terms of disability-adjusted life years (DALYs) lost, is attributable to premature death rather than illness, and prevalence and mortality can be reduced faster than incidence in chemotherapy programs. Thus, the TB death rate among Alaskan Eskimos dropped at an average of 30 percent per year in the period 1950–70 and at an average of 12 percent per year throughout the Netherlands from 1950 to 1990. Indirect assessments of the effect of DOTS suggest that 70 percent of the TB deaths expected in the absence of DOTS were averted in Peru between 1991 and 2000, and more than half the TB deaths expected in the absence of DOTS are prevented each year in DOTS provinces of China (Dye and others 2000; Suarez and others 2001). There have been few direct measures of the reduction in TB prevalence over time, but surveys done in China in 1990 and 2000 showed a 32 percent (95 percent confidence limits 9–51 percent) reduction in the prevalence rate of all forms of TB in DOTS areas, as compared with the change in the

prevalence rate in other parts of the country (China Tuberculosis Control Collaboration 2004; PRC Ministry of Health 2000). These findings imply that the targets of halving prevalence and death rates between 1990 and 2015 are technically feasible, at least in countries that are not burdened by high rates of HIV infection or drug resistance.

Many of the 182 national DOTS programs in existence by the end of 2003 have shown that they can achieve high cure rates: the average treatment success rate was 82 percent (that is, the percentage that were sputum-smear negative at the end of treatment plus the percentage that had completed treatment but for whom cure was not confirmed by sputum smear), not far below the 85 percent international target (WHO 2005). The outstanding deviations below that average were in Africa (73 percent) and some former Soviet republics (for example, 67 percent in Russia). Although the completion of treatment was almost a guarantee of cure before the spread of HIV and drug resistance, “completed” is an unsatisfactory way to report the outcome of treatment if cure is in doubt.

Although most TB patients probably receive some form of treatment, only 45 percent of all estimated new smear-positive cases were reported by DOTS programs to WHO in 2003. The case-detection rate in DOTS programs has been accelerating globally since 2000, but the annual increment must be still greater if the 70 percent target is to be reached by the end of 2005. Observations on the way DOTS is presently implemented suggest that a ceiling on case detection might be reached at about 50 to 60 percent (Dye and others 2003; WHO 2005). This fraction is about the same as the percentage of all cases reported annually to WHO from all sources (that is, from DOTS and non-DOTS programs). The problem is that, as DOTS programs have expanded geographically, they have not yet reached far beyond existing public health reporting systems.

## ALTERNATIVE AND COMPLEMENTARY APPROACHES TO THE DIAGNOSIS AND TREATMENT OF ACTIVE DISEASE

The limitations of the DOTS strategy have stimulated numerous initiatives to improve program performance (including treatment protocols for patients carrying drug-resistant bacilli or who are infected with HIV), active case finding, collaborations within and between public and private sector health services, schemes for outpatient and community-based treatment, and integration of the management of TB and other illnesses.

### Management of Drug-Resistant Disease

The higher the proportion of patients carrying drug-resistant bacilli is, the greater the need for accurate resistance testing and for the provision of alternative regimens that include at least

three drugs to which bacilli are fully susceptible. Of greatest importance is resistance to the two principal first-line drugs, isoniazid and rifampicin (that is, MDR-TB). The introduction of resistance testing, second-line drugs, longer treatment regimens (12 to 18 months), and rigorous bacteriological and clinical monitoring all increase program costs without necessarily ensuring high cure rates (equal to or greater than 85 percent). Indeed, achieving the same cure rates for MDR-TB patients as for patients carrying fully susceptible strains may not be possible. The cost-effectiveness of this component of a TB control program is therefore lower by an amount that depends on the nature of the resistance, the methods of testing and monitoring, and the choice of regimen. The higher costs and lower cure rates associated with treating drug-resistant TB are part of the argument for preventing the spread of resistance in the first place, as can be investigated with models of selection and transmission (Dye and Espinal 2001; Dye and others 2002; Dye and Williams 2000). Suarez and others (2002) have investigated the cost-effectiveness of managing drug-resistant TB in Peru, but because studies in other settings have yet to be published, an empirical overview is not yet possible. Further data will be available from studies in Estonia, the Philippines, and Russia in 2005.

### Treatment of HIV Coinfection

Antiretroviral therapy for HIV-positive individuals is unlikely to prevent a large fraction of TB cases unless treatment can be given shortly after HIV infection is acquired (Sonnenberg and others 2005; Williams and Dye 2003). In general, antiretroviral therapy is likely to be most effective, not in reducing TB incidence, but in extending the life expectancy of HIV-positive patients successfully treated for TB (Friedland and others 2004). Antiretroviral therapy and DOTS are formally synergistic, because without undergoing both together, HIV-infected TB patients have a short life expectancy, typically less than five years.

Where the prevalence of HIV infection has been rising quickly, as in eastern and southern Africa, even the most energetic programs of TB chemotherapy may not be able to reverse the rise in TB incidence. However, mathematical modeling indicates that, even in the midst of a major HIV epidemic, early detection and cure are the most cost-effective ways of minimizing TB cases and deaths (Currie and others, 2005). One reason is that DOTS programs treat all TB cases, not just those linked with HIV. The alternatives—the prevention of HIV infection, TLT, and antiretroviral therapy—are less promising strategies to control TB, at least for the coming decade, although they could be used in combination with DOTS.

### Active Case Finding

The DOTS strategy is based on passive case detection for three reasons: (a) the majority of incipient TB cases develop active

smear-positive, infectious disease more quickly than any reasonable interval between successive rounds of mass screening for TB symptoms or x-ray abnormalities; (b) the majority of patients severely ill with a life-threatening disease are likely to seek help quickly (Toman 1979); and (c) countries that have not yet implemented effective systems for passive case detection are not in a position to pursue cases more actively. The drawback of passive case finding is that the delays to diagnosis among symptomatic patients are often long, and health services never see some patients. To shorten delays and increase the proportion of cases detected, studies of risk can identify subpopulations in which TB tends to be relatively common. Systematic surveys of these subpopulations for active TB may be logistically feasible and affordable. The target populations include individuals infected with HIV, refugees (Marks and others 2001), contacts of active cases (Claessens and others 2002; Noertjojo and others 2002), health workers (Cuhadaroglu and others 2002), and drug users and prisoners (Nyangulu and others 1997). Despite the practical possibilities and the potential effect on transmission (Murray and Salomon 1998), active case finding is rarely done in high-burden countries, where the emphasis is still on implementing the basic DOTS strategy.

### **Case Finding and Treatment in the Private Sector**

It is well known that many TB patients first seek treatment from private practitioners and that diagnosis and treatment in the private sector often do not meet internationally accepted standards (Uplekar, Pathania, and Raviglione 2001). A new scheme to deliver DOTS through the private sector (Public-Private Mix DOTS) operates through the provision of free drugs, by information exchange and patient referral, and with some financial support from participating governments. Two pilot projects in Hyderabad and Delhi, India, improved case-detection rates by 26 percent and 47 percent, respectively, and maintained treatment success close to the target of 85 percent (WHO 2004b). Other such projects are under way elsewhere in India as well as in Bangladesh, Indonesia, Nepal, the Philippines, and Vietnam (WHO 2004d).

### **Outpatient and Community-Based Treatment**

Early studies of the cost-effectiveness of TB control found that full ambulatory treatment, eliminating hospitalization during the first two months (intensive phase), was cheaper and did not compromise cure rates (de Jonghe and others 1994; Murray and others 1991). Partly as a result, ambulatory treatment has become the standard of care in many high-burden countries. The natural extension, to home- and community-based treatment, has proved to be just as effective in several African settings, and even lower in cost (Adatu and others 2003; Dudley

and others 2003; Floyd and others 2003; Floyd, Wilkinson, and Gilks 1997; Moalosi and others 2003; Okello and others 2003; Sinanovic and others 2003; Vassall and others 2002; Wilkinson, Floyd, and Gilks 1997). Various schemes have been used to provide TB care in the community, in which nongovernmental organizations, volunteers (Okello and others 2003), or appointed “guardians” (Floyd and others 2003) supervise treatment, sometimes with financial incentives (Sinanovic and others 2003). Consequently, community-based care is being adopted in some countries (for example, Uganda) as standard procedure.

### **Integrated Management of Tuberculosis and Other Respiratory Illnesses**

Surveys in nine countries found that up to one-third of patients over five years of age attending primary health centers had respiratory symptoms, of whom 5 to 10 percent were TB suspects, but only 1 to 2 percent had TB (WHO 2004e). Because TB is rare among respiratory diseases, comanaging TB with other conditions has clear advantages. The purpose of the WHO’s Practical Approach to Lung Health (PAL) project is to encourage a syndromic approach to management of patients, to standardize health service delivery through the development and implementation of clinical guidelines, and to promote the necessary coordination within national health services. Preliminary investigations in the Kyrgyz Republic and Morocco suggest that PAL projects can improve the accuracy of diagnosis, encourage better practice in prescribing drugs, and strengthen primary care. However, a full analysis of costs and effects in the nine-country study remains to be done.

## **COST-EFFECTIVENESS OF INTERVENTIONS AGAINST TUBERCULOSIS**

Some questions about investing in TB control are broad and strategic (for example, should money be spent on the control of TB rather than on the control of some other condition?); others are specific and technical (for example, which laboratory diagnostic procedures should be used?). On whatever level the question is posed, cost-effectiveness analysis (CEA) has become a prominent method for evaluating and choosing among different health interventions.

### **Background**

Between 1980 and 2004, 32 studies of the cost-effectiveness of TB control were published from the low- and middle-income countries considered by the Disease Control Priorities Project (table 16.1; online annex 3 summarizes the 32 studies that have been published according to the country and year of publication, the question being addressed, the strategies compared, the

**Table 16.1** Number of Studies on the Cost-Effectiveness of TB Control by Topic and Region, 1980–2004

Intervention	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	World	Total	Number that consider transmission
BCG vaccination	1	0	0	0	0	0	0	1	0
TLTI	0	0	0	0	0	3	0	3	3
Treatment of active disease: the DOTS strategy	4	2	0	1	0	2	0	9	4
Variations on DOTS:									
Management of drug-resistant disease	0	0	1	0	0	1	0	2	1
Treatment of HIV coinfection	0	0	0	0	0	1	0	1	0
Active case finding and diagnosis	0	1	1	0	0	4	1	7	1
Outpatient and community-based treatment	0	0	0	0	2	7	0	9	0
All interventions	5	3	2	1	2	18	1	32	9

Source: Authors.

subjects and costs considered, the effectiveness of measures used, whether or not transmission is considered, and the main results and conclusions). Almost all of these studies (28, or 88 percent) have concerned ways of finding, diagnosing, and treating patients with active TB, and most (18, or 56 percent) have been done in eight countries in Sub-Saharan Africa (Floyd 2003). Three studies (all in Sub-Saharan Africa) have investigated TLTI, and one study in Indonesia has examined BCG vaccination. The principal findings are that short-course chemotherapy for active TB is a comparatively cost-effective intervention and one of the most cost-effective of all health interventions. TB patients can be treated more cheaply and conveniently outside hospitals on an ambulatory basis, by health staff or with the help of family and community members, without compromising the success of treatment. Supplementary methods, such as standardized second-line drug treatment for MDR-TB, appear to be affordable and cost-effective in some settings.

What does not emerge from this compilation of data is a comprehensive overview of the value for money provided by current and potential interventions against TB in all major regions of the world, expressed using a common measure of effectiveness and based on a consistent approach to the evaluation of transmission. (The returns on investment in infectious disease control include the immediate benefits to individuals treated—for example, those vaccinated or given drug therapy—plus the longer-term benefits gained by preventing secondary

cases through reduced transmission.) Little work has been done in China, India, and other large countries in Asia, even though Asia carries the largest burden of TB, and only limited information is available for Europe and Central Asia, Latin America and the Caribbean, and the Middle East and North Africa. Of the 32 studies, only 10 used a measure of effectiveness that allows comparison with other diseases (table 16.2), and only 9 attempted to include an estimate of the benefits gained from reduced transmission (table 16.1). The benefits from reduced transmission are usually assessed through mathematical modeling (using computer simulations) for a given epidemiological situation, an approach that produces specific solutions for each setting rather than results that are generally applicable. In addition, although the benefits from prevented transmission are lower when TB is endemic, existing studies do not make a clear distinction between the cost-effectiveness of interventions in epidemic (outbreak) and endemic situations.

## Methods

In this study, a general analytical framework was used to evaluate the total costs and total effects (defined as cases prevented, deaths averted, and DALYs gained) of the principal interventions against TB across six regions of the world (see online annexes 4–7 for further details). A dynamic infectious disease model (online annex 4) was used to derive general formulas for calculating the cost-effectiveness of interventions

**Table 16.2** Number of Studies on the Cost-Effectiveness of TB Control by Effectiveness Measure and Intervention, 1980–2004

Intervention	Cases detected or cases diagnosed	Cases prevented	Cure or successful treatment rate	Deaths prevented	Years of life saved	QALYs gained	DALYs gained
BCG vaccination	0	1	0	1	0	0	0
TLTI	0	3	0	0	0	1	0
Treatment of active disease: the DOTS strategy	0	1	6	1	3	0	1
Variations on DOTS:							
Management of drug-resistant disease	0	0	2	2	0	0	1
Treatment of HIV coinfection	0	0	0	1	0	0	0
Active case finding and diagnosis	5	0	0	0	1	0	2
Outpatient and community-based treatment	0	0	10	0	0	1	0
All interventions	5	5	18	5	4	2	4

Source: Authors.

QALY = quality-adjusted life year.

Note: The total for all interventions is greater than the number of studies because some studies use more than one measure of effectiveness.

to control endemic (online annex 5) and epidemic (online annex 6) TB in a wide variety of settings. The formulas are approximate, but they are simple and able to provide insights into the strategies that give value for money under a wide variety of epidemiological circumstances. The model was then supplied with cost and efficacy data (online annex 7) for each of the six World Bank regions for four main groups of interventions:

- immunization with BCG (proportion of infants,  $m$ , assumed to be protected against severe, noninfectious childhood TB only), or a new vaccine that prevents infection and progression to pulmonary and extrapulmonary TB in children and adults
- isoniazid treatment of latent TB infection (TLTI, given at per capita rate  $\rho$ ), for people infected with *M. tuberculosis*, with or without HIV coinfection and with or without the use of radiography to exclude patients with active disease
- short-course chemotherapy, delivered as a component of the DOTS strategy, for smear-positive or smear-negative pulmonary disease and extrapulmonary disease (with a combination of drugs given at per capita rate  $\tau$ ), and for patients infected with HIV, with or without supporting anti-retroviral therapy
- treatment for MDR-TB using a standardized regimen including first- and second-line drugs or using individualized regimens of first- and second-line drugs that are tailored to each patient's drug susceptibility pattern.

Costs were considered from a health system or provider perspective. They were calculated by combining estimates of the quantities of resources required for each intervention (per patient or per person treated) with the unit prices of those resources (in 2001 U.S. dollars) using the cost categories and unit prices defined in the Disease Control Priorities costing guidelines.

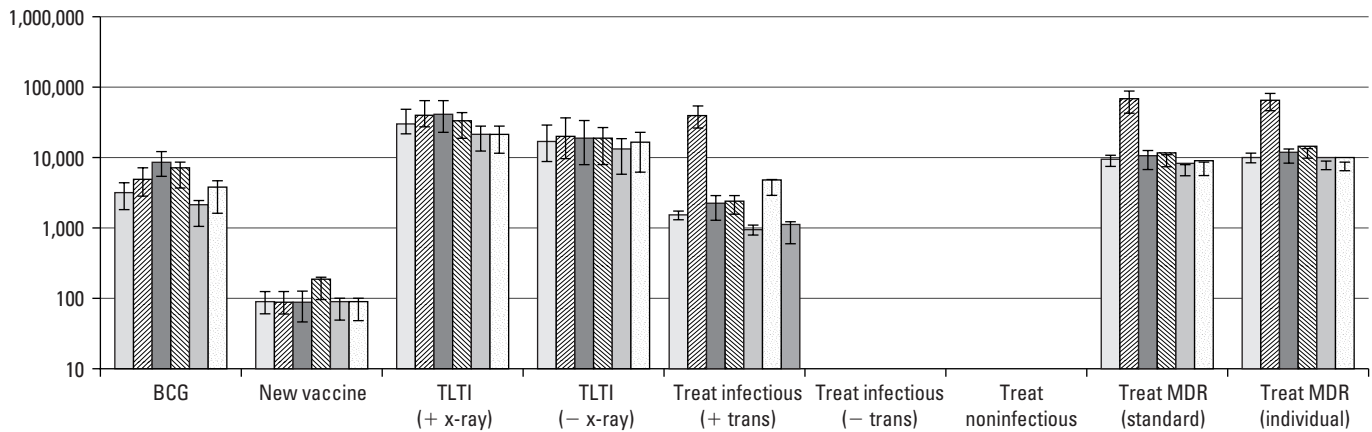
## COST-EFFECTIVENESS OF MANAGING ENDEMIC TUBERCULOSIS

The primary problem in global TB control is the management of disease in countries where incidence has been roughly stable for many years (that is, where TB is endemic).

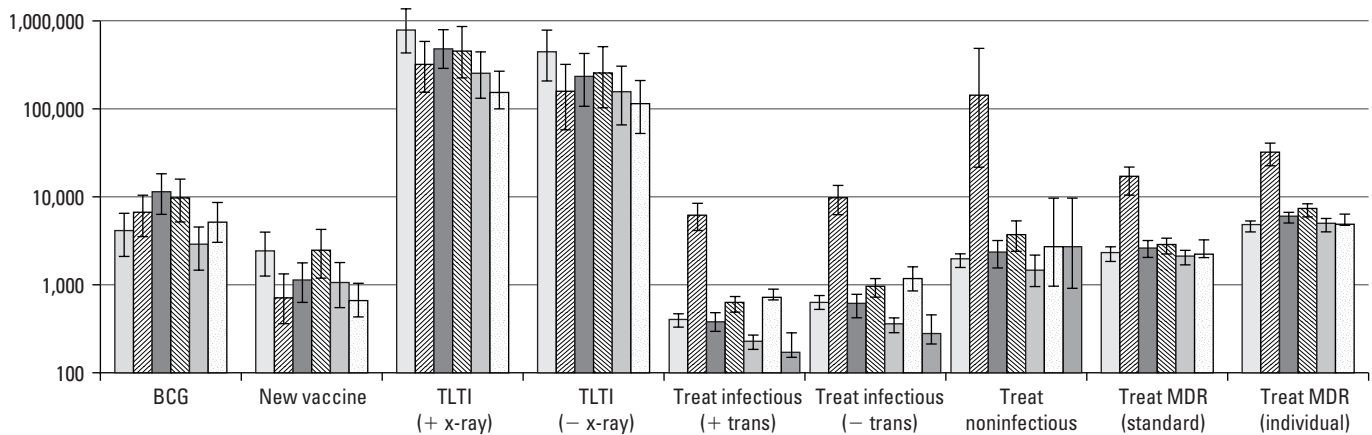
### Cost per Case Prevented

In monetary terms, the cost-effectiveness ( $C/E$ ) of a new program of treatment for active infectious disease (here defined as sputum-smear positive), per case prevented, can be calculated from  $C/E \approx P/\epsilon kT$ , where  $P$  is the cost of treatment,  $\epsilon$  is the efficacy of treatment,  $k$  is a constant determined by the mode of action of the intervention, and  $T$  is the duration of the intervention in years (online annex 5). The cost per case prevented is mostly in the range of US\$1,000 to US\$10,000, depending on the region of the world (figure 16.1). The exception is Europe and Central Asia, where costs are high because patients are currently treated for long periods in hospitals rather than on an

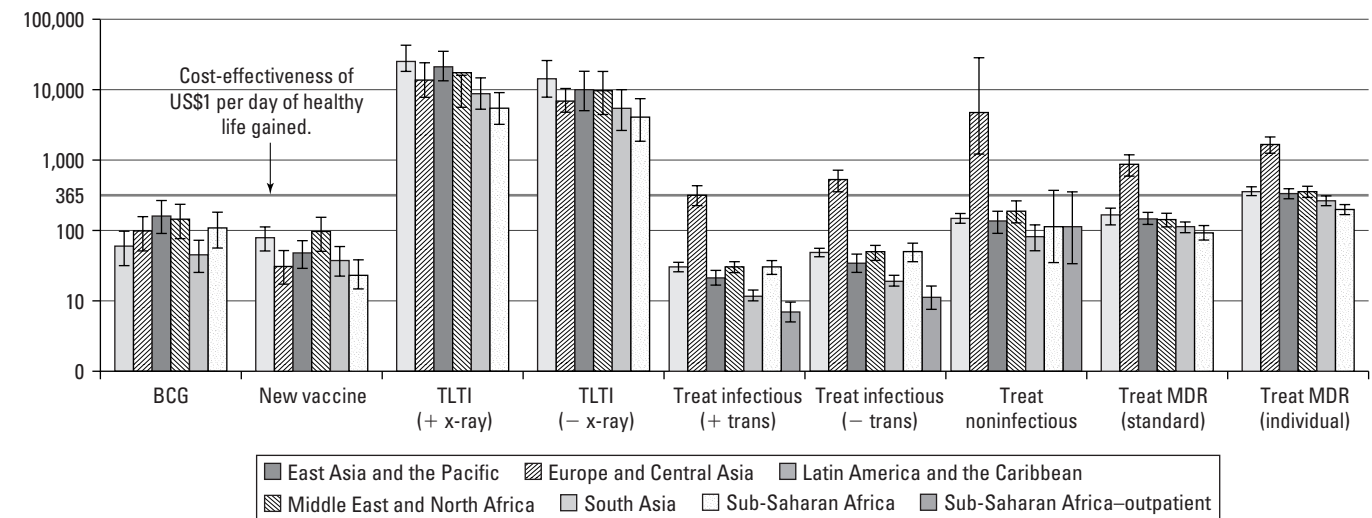
Cost per case prevented (US\$)



Cost per death prevented (US\$)



Cost per DALY gained (US\$)



Source: Authors.

Note: Where shown, bar 7 is for ambulatory (outpatient) treatment in Sub-Saharan Africa. The treatment of active disease saves no additional cases of TB when the effects of reducing transmission are excluded, so the cost per case prevented cannot be calculated. Cost-effectiveness of vaccination and TLTI is calculated for an initial incidence rate of 100 per 100,000 population per year. Cost-effectiveness ratios are plotted on a logarithmic scale. Error bars are 90 percent confidence limits. The horizontal gray line in the third chart marks a cost-effectiveness of US\$1 per day of healthy life gained.

**Figure 16.1** Cost-Effectiveness of Different Interventions against Endemic TB

ambulatory basis. These cost-effectiveness ratios (CERs) are computed from the total costs and total effects of treatment. Costs are therefore the same as the incremental costs for new programs. If costs and effects are compared with those of a previous treatment program, CERs for the treatment of active disease are often negative; that is, the program sooner or later saves money, as well as preventing TB cases. The positive CERs reported here for new treatment programs are, in this sense, upper estimates.

The cost of TLTI per active case prevented also depends on the initial incidence rate ( $I$ ) and is calculated from  $C/E \approx P/\epsilon KIT$  (online annex 5). The cost is substantially higher than that for the treatment of active TB: US\$20,000 to US\$40,000 when radiography is used to exclude patients with active disease, but it is less (US\$13,000 to US\$20,000) if active TB can be ruled out on the basis of symptoms and clinical examination (figure 16.1). TLTI is less cost effective than the treatment of active TB because preventive treatment would be given to latently infected individuals, most of whom were not recently infected and who are at small risk of developing active disease. In an endemic setting, there is no feasible method of identifying individuals who have recently acquired infection and who will proceed rapidly to active TB.

A new vaccine that prevents infection and, hence, the progression to pulmonary TB among people who were previously uninfected would be extremely competitive (US\$90 to US\$200) per case prevented if the costs were the same as those for BCG. BCG is cheap to manufacture and administer (US\$1 to US\$3 per dose) but less cost-effective (US\$2,000 to US\$8,500 per case prevented) than the treatment of active disease because it is assumed to protect against severe forms of childhood TB only and because it does not affect transmission (figure 16.1).

### Cost per Death Prevented and DALY Gained

The wider benefits of treating active TB are revealed when allowing for the additional reduction in case fatality. For a 10-year program of treatment for infectious TB, the cost per death prevented is typically US\$150 to US\$750, and the cost per DALY gained is US\$5 to US\$50 for all regions except Europe and Central Asia (figure 16.1). When TB is close to the endemic equilibrium, the extra benefits gained from reducing transmission under DOTS are small: the cost per DALY gained is only 60 percent higher when transmission benefits are excluded. The treatment of noninfectious TB is less cost-effective (US\$60 to US\$200 per DALY gained), not primarily because transmission is unaffected, but because the case fatality of untreated smear-negative and extrapulmonary disease is relatively low. Treating infectious MDR-TB is between two and ten times more costly than treating drug-susceptible TB per death prevented (greater than US\$2,000), or per DALY gained

(greater than US\$90), assuming resistant bacilli are as transmissible and pathogenic as susceptible bacilli.

BCG vaccination is not much less cost-effective than the treatment of active disease (US\$40 to US\$170 per DALY gained; higher where the risk of infection is lower). If a new vaccine with 75 percent efficacy against pulmonary disease and other forms of TB costs the same as BCG, it would be almost as cost-effective (US\$20 to US\$100 per DALY gained) as the ambulatory treatment of active TB. As expected from the preceding analysis, TLTI is much more expensive than all other options (US\$5,500 to US\$26,000 per DALY gained) and most costly where the death rate from TB among adults is already relatively low—for example, because an effective DOTS program already exists. Although the cost-effectiveness of each intervention varies among regions, the variation among strategies is much greater, whatever the outcome measure (figure 16.1).

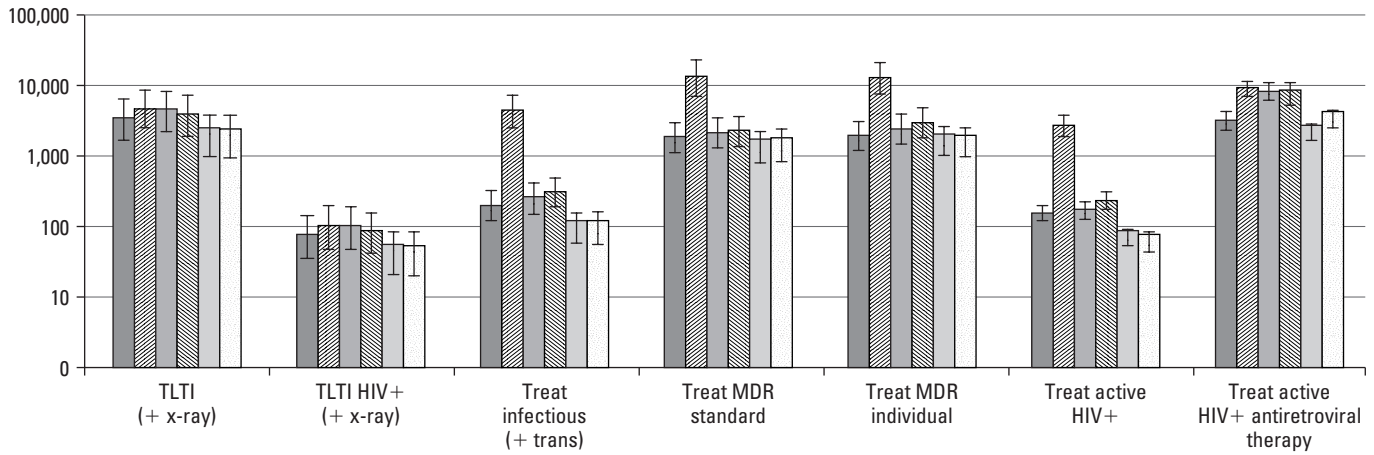
## COST-EFFECTIVENESS OF MANAGING TUBERCULOSIS OUTBREAKS

The basic case reproduction number,  $R_0$ , is a ready-made epidemiological tool for relating effort and reward in the management of outbreaks.  $R_0$  is the average number of secondary cases generated by a primary case introduced into a previously uninfected population (Anderson and May 1991). No country is presently free of TB, but some countries have recently suffered “epidemic” increases in incidence from previously low levels. The algebraic expression of  $R_0$  for TB reveals how the various components of a disease’s natural history and the different kinds of intervention interact with each other to influence transmission and the generation of new cases (online annex 4). For example, the cost-effectiveness of chemotherapy per *M. tuberculosis* generation is  $C/E = P\sigma\tau/\epsilon R_0$ , where  $\tau$  is the number of TB patients treated per prevalent case per unit time, and  $\sigma$  is the proportion of new cases that is infectious.

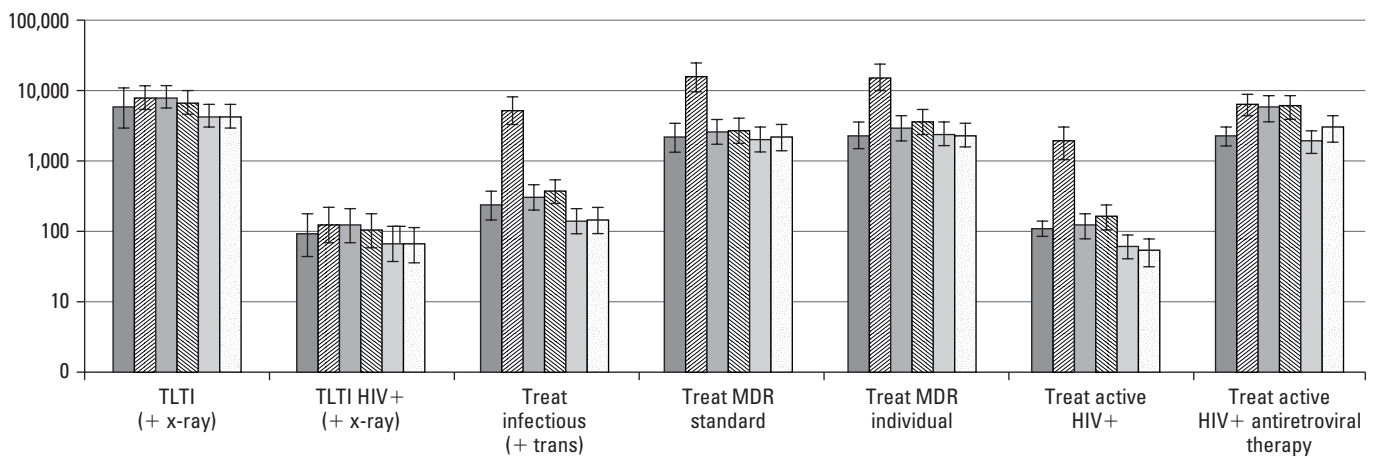
The biggest resurgences of TB in recent history have been driven by the spread of HIV in Africa and are linked to the rise of drug resistance in former Soviet republics; this analysis is confined to interventions associated with these two phenomena (figure 16.2; online annex 6). Indeed, in this study, interventions related to TB with HIV are considered only in the epidemic context.

If multidrug-resistant strains of *M. tuberculosis* are assumed to have the same intrinsic transmissibility and pathogenicity as drug-susceptible strains, and given the spread of MDR-TB as an independent epidemic (Dye and Williams 2000), then treatment of MDR-TB with a standard regimen including second-line drugs is more costly per DALY gained than treatment of fully susceptible disease in Sub-Saharan Africa, but it is marginally less costly than TLTI (with an x-ray screen) over most rates of case detection and treatment (online annex 6).

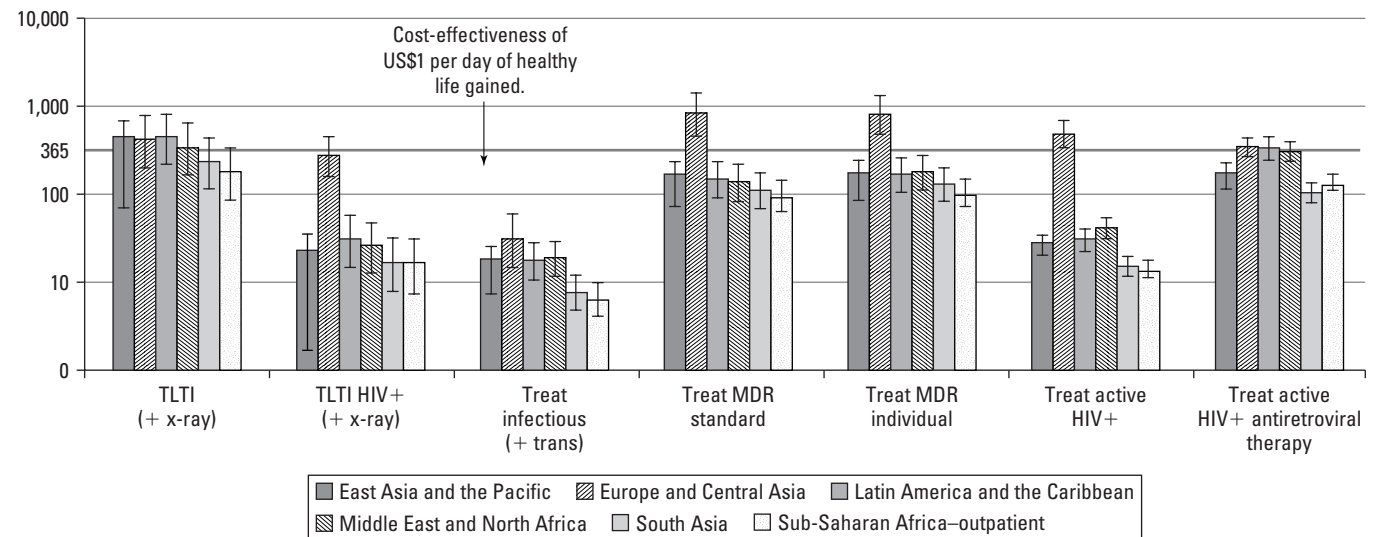
Cost per case prevented (US\$)



Cost per death prevented (US\$)



Cost per DALY gained (US\$)



Source: Authors.

Note: Five interventions used in the management of TB epidemics that are linked with HIV and MDR-TB (TLTI for people coinfecting with TB and HIV, treatment of infectious MDR-TB with a standard or individual regimen, treatment of HIV-infected TB patients with TB drugs, treatment of HIV-infected TB patients with TB and antiretroviral drugs) are compared with two standard methods (TLTI, with active disease excluded by x-ray screen, and treatment of active infectious disease, allowing for transmission). Cost-effectiveness ratios (plotted on a logarithmic scale) vary with the treatment rate (online annex 6); for illustration here, 20 percent of eligible people are treated annually with each intervention. The horizontal gray line in the third figure marks a cost-effectiveness of US\$1 per day of healthy life gained. Error bars are 90 percent confidence limits.

Figure 16.2 Cost-Effectiveness of Managing Epidemic TB

For example, at the fixed rate of treatment used to generate figure 16.2, treatment of MDR-TB with a standard regimen costs US\$91 to US\$846 per DALY gained, depending on the region, as compared with US\$6 to US\$31 for the treatment of drug-susceptible TB. The treatment of MDR-TB with regimens tailored to the resistance patterns of individual patients is more costly but also more efficacious than standardized treatment for MDR-TB and, therefore, almost equally cost-effective under this set of assumptions.

TB patients infected with HIV are more costly to treat per DALY gained than HIV-negative patients, either without antiretroviral therapy (low cost, short life expectancy) or with such therapy (high cost, long life expectancy). TLTI is a more attractive option for the management of epidemic TB than for endemic TB (compare figures 16.1 and 16.2), because during an outbreak, TLTI is directed at recent rather than remote infection. TLTI is even more cost-effective in the control of TB and HIV coinfection, because it prevents the rapid breakdown to active disease caused by immunodeficiency.

These results are indicative rather than definitive, because the calculations assume, among other things, that HIV-infected populations exist in isolation; in reality, HIV-infected people also acquire TB infection from TB patients who are not infected

with HIV. Neither does this analysis address all the important questions about managing outbreaks of drug-resistant or HIV-related TB. Fuller investigations should assess, for example, the benefits to whole populations of giving antiretroviral therapy to HIV-infected individuals before they develop TB and of investing in DOTS to prevent multidrug-resistant epidemics from arising in the first place.

## SUMMARY OF COST-EFFECTIVENESS ANALYSES

Box 16.1 summarizes the results of these calculations of the cost-effectiveness of managing epidemic and endemic TB. The findings are one justification for maintaining and expanding DOTS programs, on the basis of SCC for patients with active disease, as the dominant mode of TB control around the world. BCG vaccination and the treatment of MDR-TB (standard or individualized regimens) or HIV-infected TB patients (with or without supporting antiretroviral therapy) are more costly in absolute terms, but they typically cost less than US\$1 per day of healthy life gained, which is less than the average economic productivity of workers in the least developed countries. TLTI appears to be relatively poor value for money, even though this analysis assumes that one course of treatment prevents active

### Box 16.1

#### Cost-Effectiveness of TB Interventions: Main Findings

- The cost effectiveness of TB control depends not only on local costs but also on the local characteristics of TB epidemiology (for example, epidemic or endemic, low or high rates of HIV infection and drug resistance) and on the rate of application of any chosen intervention.
- Short-course chemotherapy for the treatment of infectious and noninfectious TB patients through the DOTS strategy is highly cost-effective for the control of either epidemic or endemic TB (US\$5 to US\$50 per DALY gained, for regions excluding Eastern and Central Europe). When a new treatment program is compared with a previous program, DOTS often saves money as well as preventing cases and deaths.
- Some variations on DOTS are less cost-effective but still good value for money, including the treatment of patients with MDR-TB (standard or individualized drug regimens) and with HIV infection (with or without supporting antiretroviral therapy). For these additional interventions, the cost per DALY gained is less than the annual average economic productivity per capita in the least developed countries.
- Even with relatively favorable assumptions, the treatment of latent TB infection where TB is endemic and populations are unaffected by HIV is the least cost-effective of the interventions examined here (US\$5,500 to US\$26,000 per DALY gained). TLTI is more cost-effective during outbreaks (US\$150 to US\$500 per DALY gained) and for people who are coinfecting with TB and HIV (US\$15 to US\$300 per DALY gained).
- BCG vaccination to prevent severe forms of childhood TB is much less effective than SCC but nearly as cost-effective (US\$40 to US\$170 per DALY gained).
- A new vaccine that prevents pulmonary TB with high efficacy (equal to or greater than 75 percent) would be more cost-effective than BCG if the cost of immunization were the same as BCG (US\$20 to US\$100 per DALY gained).
- For any intervention with the potential to cut transmission (that is, excluding BCG vaccination), control of epidemic disease produces more favorable cost-effectiveness ratios than control of endemic disease, because the benefits gained from reduced transmission are greater during outbreaks.

Source: Authors.

TB for life. TLTI is more cost-effective in epidemic than in endemic settings, and it is more cost-effective when it is used to treat individuals coinfecting with TB and HIV. A new, high-efficacy vaccine that prevents infection and the progression to pulmonary TB in adults, to be directed at the control of endemic TB, would be more cost-effective than BCG at the same price and almost as cost-effective as SCC.

### Averted and Avertable Burden of Tuberculosis

Trends in case notifications can be used, judiciously, to assess regional and global trends in TB incidence, but no satisfactory large-scale analysis has been done of the number of cases prevented by chemotherapy (as distinct from the reductions in transmission and susceptibility associated with improved living standards). One approach to evaluating the averted and avertable burden of TB begins with the observation that 86 percent of the years of healthy life lost that are attributable to TB are from premature death, and only 14 percent are from illness. Because DALYs lost are dominated by premature death, a conservative estimate of the burden of TB alleviated can be obtained in terms of the number of deaths and associated DALYs gained, regionally and globally, since the introduction of the DOTS strategy in 1991.

Figure 16.3 is derived from recent estimates of cases and deaths and their trends by region, including those attributable to HIV coinfection (Corbett and others 2003; WHO 2004c). In the MDG baseline year, 1990, approximately 1.5 million TB deaths (28 per 100,000) occurred. BCG vaccination saved roughly 650,000 deaths from extrapulmonary TB among

children between 1990 and 2003. If chemotherapy is assumed to reduce only the case-fatality rate and to have no effect on transmission and incidence, 23 million deaths (44 percent) would have been saved in non-DOTS treatment programs. The expansion to 45 percent case-detection rate under DOTS during the same period saved an estimated 2.3 million (≈5 percent) additional deaths, the largest numbers in Sub-Saharan Africa (1.1 million), East Asia and the Pacific (558,000), and South Asia (408,000). Further analysis shows that, if 70 percent of TB cases (smear positive and smear negative) can be treated under DOTS before MDG target year 2015, an estimated 1.9 million TB deaths (26 per 100,000) will occur in that year, a greater number than in 1990, but a 7 percent lower death rate per capita (Dye and others 2005).

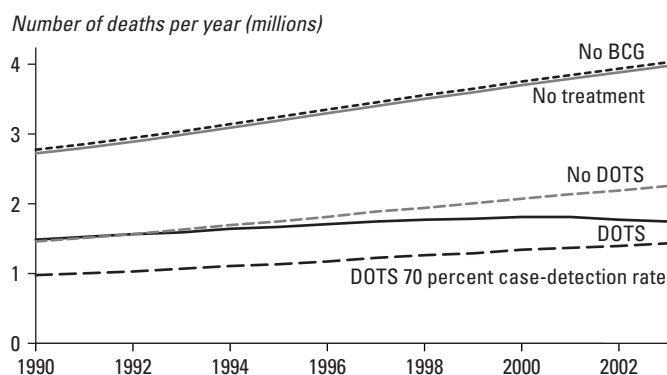
The calculations for Africa assume that treatment cures TB in the majority of HIV-infected patients even though, without antiretroviral therapy, many of these patients will die anyway. Despite these favorable assumptions, the number of TB deaths was evidently still rising in Africa in 2003, whereas it was falling in Asia, aided by the large programs of DOTS expansion in China (1991–97) and India (from 1998).

Reducing the TB death rate sufficiently to meet the MDG target requires a significant cut in incidence, as well as in case fatality. An extension of this assessment suggests that case detection must reach at least 70 percent and the TB incidence rate must fall by 5 to 6 percent annually between 2003 and 2015 (Dye and others 2005). For the world, excluding Sub-Saharan Africa and former Soviet republics, the incidence rate would have to fall at a more modest 2 percent per year.

New diagnostics, drugs, and vaccines would also help reduce the global TB burden more quickly. The most desirable of these is a vaccine that prevents pulmonary disease, whether or not vaccination subjects are already infected (a pre- or postexposure vaccine), and that confers lifetime immunity (Andersen 2001; Fordham von Reyn and Vuola 2002; McMurray 2003; Young and Stewart 2002). A new vaccine with high efficacy against pulmonary TB would almost certainly change immunization practice: mass vaccination campaigns among adults (rather than infants) would have dramatic effects, going far beyond the expectations of DOTS programs (figure 16.4; Dye 2000). A postexposure vaccine that stops progression to disease among those already infected, as well as preventing infection in others, would have greater effect than a preexposure vaccine that only prevents infection (Lietman and Blower 2000). However, such calculations are at present highly speculative, because the mode of action and efficacy of any new vaccine is unknown.

### Economic Benefits of Tuberculosis Control

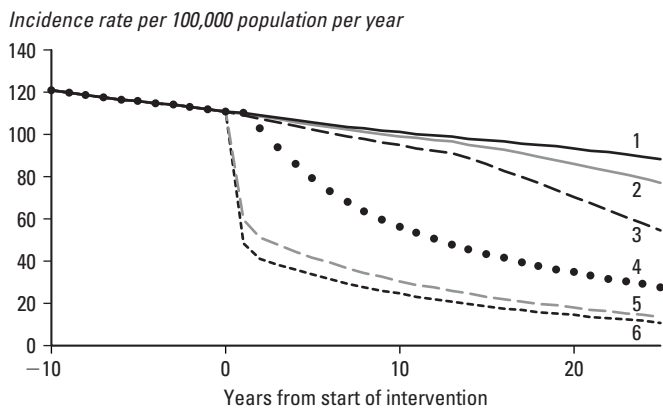
Preventing TB deaths brings no savings in the costs of TB control unless it is accompanied by a reduction in incidence so that fewer patients require treatment. The prompt and effective



Source: Authors.

Note: Broken and gray lines represent various hypothetical scenarios; the solid black line represents DOTS programs. The interventions are, from top to bottom: no BCG vaccination and no anti-TB treatment, no treatment, no DOTS programs, DOTS expansion from zero to 45 percent case detection over the period 1990–2003, and DOTS with 70 percent case-detection rate throughout the period 1990–2003. To make a conservative assessment of effect, the treatment of active TB is assumed to change the case-fatality rate without affecting the TB incidence rate.

**Figure 16.3** Estimated Number of TB Deaths Worldwide under Various Hypothetical Scenarios and the Estimated Effect of DOTS Programs, 1990–2003



Source: Dye 2000.

Note: Lines and points show: (1) no intervention in a population where TB is already in slow decline, as in many countries in Asia and Latin America; (2) a postexposure vaccine given annually to infected infants so that 20 percent are immunized; (3) a postexposure vaccine given annually to infected infants so that 70 percent are immunized; (4) DOTS reaching 70 percent case detection and 85 percent cure by year 5 and maintained at these levels thereafter; (5) one-time mass immunization with a preexposure vaccine giving 70 percent protection to uninfected people, followed by annual vaccination of infants with the same fraction protected; and (6) one-time mass immunization with a postexposure vaccine giving 70 percent protection to uninfected people, followed by annual vaccination of infants with the same fraction protected.

**Figure 16.4** Hypothetical Effect of New Vaccines on TB Incidence Rate

treatment of active disease is almost certainly reducing transmission around the world, but because the effect on incidence is necessarily slow, it has been hard to quantify in all but a few countries, notably Peru (Suarez and others 2001).

The monetary savings implied by a reduction in incidence of one-quarter (26 percent) between 2000 and 2015—which may be enough to achieve the MDG targets—could be magnified or diminished by adjustments to the DOTS strategy. On the one hand, without compromising cure rates, chemotherapy can be delivered more cheaply to outpatients than inpatients and with less reliance on x-ray diagnosis and surgical procedures. On the other hand, various additions to DOTS—contact tracing, active case finding, antiretroviral therapy for HIV-infected patients, second-line drugs for patients carrying resistant bacilli, or joint public-private schemes for the management of TB—might be desirable but more costly per year of healthy life gained. Whether the savings made by reducing incidence and improving efficiency offset the costs of DOTS add-ons will, therefore, depend on the setting.

Besides the possibility of reducing diagnostic and treatment costs, improved health and longevity yield other economic benefits, but the quantification of those benefits is always controversial. This difficulty is reflected in the limited number of cost-benefit analyses of TB control; among the few examples, one detailed study in India estimated the potential societal benefits of DOTS to be worth US\$8.3 billion in 1993–94, or 4 percent of the gross domestic product (Dholakia 1996). Without attempting to extend such analyses here, we note that the preceding results also imply that large-scale treatment programs

for TB are likely to give net returns on investment or at least to appear to be good value for money in ways that go beyond the arguments from cost-effectiveness (Jack 2001).

The analysis earlier in this chapter showed that SCC typically costs up to US\$30 per DALY gained for the treatment of infectious TB and up to US\$200 per DALY gained for the treatment of noninfectious TB (excluding Europe and Central Asia). These figures can be compared with a recent estimate of US\$1.5 billion as the annual global cost of treating 70 percent of cases with 85 percent cure (WHO 2004c). Reaching these targets would prevent approximately 2.1 million of all the TB deaths expected if no treatment were available in 2003, including 391,000 deaths prevented by DOTS (figure 16.3). Because each TB death prevented gains approximately 20 DALYs (WHO 2002b), the total cost per DALY gained would be about US\$36. This rough calculation excludes any benefits in reduced transmission but includes the costs of treating smear-negative and extrapulmonary TB and is of the same order of magnitude as the results from CEA.

However the calculation is done, the cost of gaining a year of healthy life under DOTS is substantially less than the annual average productivity per capita in the low-income (gross national income [GNI] less than or equal to US\$735) or least developed (GNI average US\$290, <http://www.worldbank.org>) countries, and it is probably less than the marginal productivity of labor in the poorest communities. It is also less than twice the average annual income per capita, which has also been proposed as a benchmark for assessing whether an intervention is cost-effective (Garber and Phelps 1997). Moreover, it is less than the World Bank's definition of *absolute poverty* (living on US\$1 per day or less, close to average GNI per capita for the least developed countries) and is certainly less than the monetary values that are typically placed on the value of a human life year (for example, a life was valued at US\$100,000 by the 2004 Copenhagen Consensus panel, <http://www.copenhagenconsensus.com>). All these comparisons suggest not only that the basic DOTS strategy, and perhaps even an enhanced DOTS strategy, are cost-effective but that they also have very favorable cost-benefit ratios.

## RESEARCH AND DEVELOPMENT

The preceding review and analysis suggest at least six areas for economic and epidemiological research and development:

1. *DOTS expansion.* Refinement of existing cost estimates of scaling up DOTS programs to reach and move beyond targets for case detection (70 percent) and cure (85 percent) in the poorest countries—notably in Africa—through more comprehensive planning and budgeting exercises. The analyses should include the costs of developing fully staffed

health services, with expanded and renovated infrastructure and improved management capacity where necessary, and the costs of the new initiatives that will be required to improve case detection and cure rates.

2. *Service delivery.* Assessment of the potential for health service restructuring to detect, diagnose, and treat TB patients more efficiently through syndromic management of respiratory diseases at primary health centers and through collaborations between public and private health services, between different parts of the public sector health service, and between TB and HIV/AIDS control programs.
3. *Complementary strategies.* Further investigation of the costs and effectiveness of strategies that are potentially complementary to DOTS, including active case finding and TLTI in high-risk populations, and the management of drug resistance and of patients infected with HIV.
4. *Impact and targets.* Evaluation of the actual and potential effects of the tools (mostly drugs) now being used for TB control. This research requires a better understanding of the ways human population density, age structure, migration, HIV coinfection, and drug resistance affect TB epidemiology. The analyses should check the internal consistency of international targets for the implementation and effect of chemotherapy programs, as defined by the MDGs. The analyses should also make better use of the rich body of routine surveillance data collected by all national TB control programs around the world.
5. *Risk factors.* Assessment of the reductions in TB cases and deaths that could be made by reducing exposure to environmental risk factors, notably indoor and outdoor air pollution, tobacco smoking, and malnutrition. These risk factors affect the establishment of infection, the progression to active disease, and the outcome of treatment.
6. *New diagnostics, drugs, and vaccines.* A sensitive and specific test for active TB that is cheap and simple to use at the first point of contact between patients and health services would be a major advance in diagnosis. Mycobacterial culture, which detects a higher proportion of active TB patients than sputum-smear microscopy, is a prerequisite for screening for drug resistance. However, present culture methods are slow, taking four to six weeks to obtain a result. Technology based on phage amplification and nucleic acid amplification can establish whether cultures are positive in days or hours, but this technology needs to be packaged for use in developing countries (Albert and others 2002, 2004; Johansen and others 2003; Woods 2001). The tuberculin skin test is being superseded in many developed countries by more specific methods for detecting infection (Doherty and others 2002; Pai, Riley, and Colford 2004). A test that can predict who will progress from latent to active disease, as yet hypothetical, would greatly increase the feasibility of treating latent infection.

Among a growing list of new vaccine antigens (Fruth and Young 2004), three of the most promising are now undergoing phase 1 safety trials in humans. One trial has evaluated mycobacterial antigen 85, delivered as a recombinant smallpox vaccine (Goonetilleke and others 2003). Another is testing a live attenuated BCG bacterium (rBCG30) that overexpresses antigen 85B protein and that provides guinea pigs with greater protection than BCG alone (Horwitz and others 2000). A third trial is assessing a fusion protein of two different antigens in adjuvant, referred to as Mtb72f, that is likely to be used as a booster to either BCG or rBCG30 (Reed and others 2003). Compounds that could form the basis of new drugs and new drug regimens include the nitroimidazopyran PA-824. Experiments with a mouse model of TB have shown that PA-824 has bactericidal activity similar to that of isoniazid and sterilizing activity that may rival that of rifampicin and that it is particularly active against dormant bacilli.

Among the most important recent discoveries is a diarylquinoline with a novel mode of action on the ATP synthase of *M. tuberculosis* that powerfully inhibits both drug-sensitive and drug-resistant strains of bacilli (Andries and others 2004). Alongside these laboratory studies, analytical and operational research are needed to find out what kinds of new tools will give the best returns on investment. Investigations of this kind will contribute to the introduction of new vaccines, drugs, and diagnostics and will inform the work of the Foundation for Innovative New Diagnostics (<http://www.finddiagnostics.org>), the Global Alliance for TB Drug Development (<http://www.tballiance.org>), and the AerasGlobal TB Vaccine Foundation (<http://www.aeras.org>).

## CONCLUSIONS

After more than a decade of climbing incidence rates in Africa and former Soviet republics, the global TB epidemic appears once again to be on the threshold of decline. The spread of HIV and drug resistance, respectively, in those two regions has exacerbated the problems of TB control, but at the same time it has helped keep TB on the international public health agenda. The global incidence rate was still rising in 2003, but more slowly each year. This slowdown is not only (or even mainly) because of direct intervention through DOTS programs but because HIV epidemics are approaching peak levels in Africa and because incidence is now starting to fall again in some former Soviet republics, including Russia. Where TB incidence is already falling, prevalence and death rates should be dropping more quickly, although little evidence demonstrates this decrease yet.

The prompt diagnosis and treatment of active TB has been the mainstay of TB control and will continue to be so for the foreseeable future. Short-course chemotherapy, delivered

through the DOTS strategy, is, at typically US\$5 to US\$350 per DALY gained, the most cost-effective among current methods for the management of TB, and in most high-burden countries, the cost is toward the lower end of this range. A comparison of the costs of treating active TB with the costs of running a previous program suggests that DOTS could actually save money in the long run. In addition, DOTS provides an operational framework for the introduction of more specialized methods in certain risk groups. The extensions to DOTS investigated here include the treatment of MDR-TB with second-line drugs, preventive therapy (TLTI) during outbreaks and for people coinfecting with *M. tuberculosis* and HIV, and antiretroviral therapy for HIV-infected TB patients. Those interventions cost more than the basic DOTS strategy but are still less than a dollar for each day of healthy life gained, which provides an economic argument for their integration into enhanced DOTS programs.

Although the analyses in this chapter show that DOTS and its extensions are good value for money, they conceal various features of health systems, as yet poorly defined, that may facilitate the implementation of treatment programs. For example, if broader investment in the health sector is needed before TB control programs can work in some parts of some countries, then the full cost of DOTS could be greater. By contrast, a more integrated approach to the management of TB and other respiratory diseases in primary health facilities could lead to cost savings. Those possibilities have not yet been investigated.

The only development that could radically alter the current approach to TB control—shifting the emphasis from cure to prevention—is the discovery of a new vaccine that protects adults against infectious pulmonary disease. Whether such a vaccine would be more or less cost-effective than BCG (US\$40 to US\$1,600 per DALY gained) depends on price and efficacy, but the potential epidemiological effect would be far greater than that of BCG, perhaps justifying mass adult vaccination. If research and development proceed according to plan, a new vaccine of some kind could be licensed between 2010 and 2015. New drugs and diagnostics should be available earlier, shortening the delay to, and duration of, treatment.

Although cost-effectiveness studies show that DOTS is a good investment, they do not formally show that the strategy is affordable. The analytical difficulty is that CEA does not solve the practical problem of how to allocate money to TB control in combination with other interventions, or even how to combine different approaches to TB control (Tan-Torres Edejer and others 2004). Interpreted literally, CEA says that the best return on total investment is obtained by ranking interventions according to CER and then fully implementing each intervention, from smallest to largest CER, allowing for diminishing returns, until the total budget is spent. This method is unlikely to lead to a balanced health care portfolio in the poorest countries. Besides, the evidence is rarely available to carry out

such a complete analysis. The results of CEA are therefore typically used more informally, along with other evidence and constraints, when a mix of health interventions is chosen.

Although this problem will recur in discussions about allocating health budgets, the case for large-scale programs of TB treatment has now been accepted in many parts of the world. That is the fruit of more than 10 years' work on burden, cost, efficacy, effectiveness, and cost-effectiveness. The governments of the less poor members of the group of 22 high-burden countries have demonstrated that they can budget for, and provide, most of the funds needed to reach target levels of case detection and cure (WHO 2004c, 2005). Some of the poorer countries among the 22 are now receiving sufficient external assistance to fill the gaps in their budgets for TB control, principally from the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Consequently, the total reported budget deficit for the high-burden countries in 2005 was remarkably small—just US\$119 million—and concentrated in the poorest countries (WHO 2005).

From those findings and observations arise two key questions for global TB control: If the estimated budget gap is filled, would the money be enough to ensure that enhanced DOTS programs reach 70 percent case detection and 85 percent cure—and by when? And if those targets are reached, will the effort be sufficient to achieve the MDG objectives of halving prevalence and death rates by 2015?

As yet, there are only partial answers. On the costs, it is clear that, by moving treatment out of hospitals and into the community, DOTS can often be made cheaper and more convenient for patients and health services without compromising treatment outcome. However, planning for TB control in the poorest countries is still inadequate, and budgets commonly understate the real costs of scaling up national TB control programs (WHO 2004c, 2005). Despite those weaknesses in the budgeting and funding process, the overall expenditure on TB control in high-burden countries has increased since 2000, and the injection of extra effort and money has led to a small acceleration in case finding globally. As a result, case detection under DOTS could reach 50 to 60 percent by 2005, and treatment success should be close to the target level of 85 percent.

A case-detection rate of 50 to 60 percent may not be enough. The analysis in this chapter suggests that the MDG objective of halving the death rate can be reached with 70 percent case detection globally, provided this case detection also generates a 5 to 6 percent annual reduction in the incidence rate between 2003 and 2015. The DOTS program in Peru generated a 6 to 7 percent annual reduction in the incidence rate of pulmonary TB, but that result has not yet been repeated in other high-burden countries with good control programs (for example, India, Morocco, and Vietnam). It is unlikely to be achieved in African countries that currently have high rates of HIV infection.

Although others have emphasized that the costs of infectious disease control can be related to the benefits in complex ways (Brandeau, Zaric, and Richter 2003), we advocate the use of a powerful new method of carrying out CEA, which is based on the observation that mathematical models can be used to generate simple (albeit approximate) and general formulas that relate reward to effort in the management of both epidemic (based on  $R_0$ ) and endemic (based on dynamics in the vicinity of equilibrium) TB. The results are similar to those obtained by using more complex simulations in specific settings, and they are accurate enough to offer a choice between interventions (Currie and others, 2005). The generality of the method exposes more clearly the reasons some interventions are comparatively cost-effective and indicates the range of conditions under which specific cost-effectiveness results apply. The scope for using this approach for other infectious diseases remains to be explored, but it should be readily applicable in the evaluation of new approaches to TB control, whether through vaccination, drug treatment, the reduction of environmental risks, or improved service delivery.

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## REFERENCES

- Aaron, L., D. Saadoun, I. Calatroni, O. Launay, N. Memain, V. Vincent, and others. 2004. "Tuberculosis in HIV-Infected Patients: A Comprehensive Review." *Clinical Microbiology and Infection* 10: 388–98.
- Adatu, F., R. Odeke, M. Mugenyi, G. Gargioni, E. McCray, E. Schneider, and D. Maher. 2003. "Implementation of the DOTS Strategy for Tuberculosis Control in Rural Kiboga District, Uganda, Offering Patients the Option of Treatment Supervision in the Community, 1998–1999." *International Journal of Tuberculosis and Lung Disease* 7: S63–71.
- Albert, H., A. Heydenrych, R. Brookes, R. J. Mole, B. Harley, E. Subotsky, and others. 2002. "Performance of a Rapid Phage-Based Test, FASTPlaque/TBTM, to Diagnose Pulmonary Tuberculosis from Sputum Specimens in South Africa." *International Journal of Tuberculosis and Lung Disease* 6 (6): 529–37.
- Albert, H., A. Trollip, T. Seaman, and R. J. Mole. 2004. "Simple, Phage-Based (FASTPlaque) Technology to Determine Rifampicin Resistance of *Mycobacterium tuberculosis* Directly from Sputum." *International Journal of Tuberculosis and Lung Disease* 8: 1114–19.
- Andersen, P. 2001. "TB Vaccines: Progress and Problems." *Trends in Immunology* 22: 160–68.
- Anderson, R. M., and R. M. May. 1991. *Infectious Diseases of Humans: Dynamics and Control*. Oxford, U.K.: Oxford University Press.
- Andries, K., P. Verhasselt, J. Guillemont, H. W. Gohlmann, J. M. Neefs, H. Winkler, and others. 2004. "A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*." *Science* 307: 223–27.
- Asamoah-Odei, E., J. M. Garcia Calleja, and J. T. Boerma. 2004. "HIV Prevalence and Trends in Sub-Saharan Africa: No Decline and Large Subregional Differences." *Lancet* 364: 35–40.
- Behr, M. A., S. A. Warren, H. Salamon, P. C. Hopewell, A. Ponce de Leon, C. L. Daley, and P. M. Small. 1999. "Transmission of *Mycobacterium tuberculosis* from Patients Smear-Negative for Acid-Fast Bacilli." *Lancet* 353: 444–49.
- Borgdorff, M. W., N. J. Nagelkerke, C. Dye, and P. Nunn. 2000. "Gender and Tuberculosis: A Comparison of Prevalence Surveys with Notification Data to Explore Sex Differences in Case Detection." *International Journal of Tuberculosis and Lung Disease* 4: 123–32.
- Bourdin Trunz, B., P. E. M. Fine, and C. Dye. Forthcoming. Global Impact of BCG Vaccination on Childhood Tuberculous Meningitis and Miliary Tuberculosis.
- Brandeau, M. L., G. S. Zaric, and A. Richter. 2003. "Resource Allocation for Control of Infectious Diseases in Multiple Independent Populations: Beyond Cost-Effectiveness Analysis." *Journal of Health Economics* 22: 575–98.
- Bucher, H. C., L. E. Griffith, G. H. Guyatt, P. Sudre, M. Naef, P. Sendi, and M. Bategay. 1999. "Isoniazid Prophylaxis for Tuberculosis in HIV Infection: A Meta-Analysis of Randomized Controlled Trials." *AIDS* 13: 501–7.
- China Tuberculosis Control Collaboration. 2004. "The Effect of Tuberculosis Control in China." *Lancet* 364: 417–22.
- Claessens, N. J. M., F. F. Gausi, S. Meijnen, M. M. Weismuller, F. M. Salaniponi, and A. D. Harries. 2002. "High Frequency of Tuberculosis in Households of Index TB Patients." *International Journal of Tuberculosis and Lung Disease* 6: 266–69.
- Cohn, D. L. 2003. "Treatment of Latent Tuberculosis Infection." *Seminars in Respiratory Infections* 18: 249–62.
- Cohn, D. L., and W. M. El-Sadr. 2000. "Treatment of Latent Tuberculosis Infection." In *Tuberculosis: A Comprehensive International Approach*, ed. L. B. Reichman and E. S. Hershfield, 471–502. New York: Marcel Dekker.
- Comstock, G. W. 2000. "How Much Isoniazid Is Needed for Prevention of Tuberculosis among Immunocompetent Adults? In Reply." *International Journal of Tuberculosis and Lung Disease* 4: 485–86.
- Comstock, G. W., C. Baum, and D. E. Snider. 1979. "Isoniazid Prophylaxis among Alaskan Eskimos: A Final Report of the Bethel Isoniazid Studies." *American Review of Respiratory Disease* 119: 827–30.
- Comstock, G. W., V. T. Livesay, and S. F. Woolpert. 1974. "The Prognosis of a Positive Tuberculin Reaction in Childhood and Adolescence." *American Journal of Epidemiology* 99: 131–38.
- Corbett, E. L., S. Charalambous, V. M. Moloi, K. Fielding, A. D. Grant, C. Dye, and others. 2004. "Human Immunodeficiency Virus and the Prevalence of Undiagnosed Tuberculosis in African Gold Miners." *American Journal of Respiratory Critical Care Medicine* 170: 673–79.
- Corbett, E. L., R. W. Steketee, F. O. ter Kuile, A. S. Latif, A. Kamali, and R. J. Hayes. 2002. "HIV-1/AIDS and the Control of Other Infectious Diseases in Africa." *Lancet* 359: 2177–87.
- Corbett E. L., C. J. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Raviglione, and C. Dye. 2003. "The Growing Burden of Tuberculosis: Global Trends and Interactions with the HIV Epidemic." *Archives of Internal Medicine* 163: 1009–21.
- Cuhadaroglu, C., M. Erelel, L. Tabak, and Z. Kilicaslan. 2002. "Increased Risk of Tuberculosis in Health Care Workers: A Retrospective Survey at a Teaching Hospital in Istanbul, Turkey." *BioMed Central Infectious Diseases* 2: 14.
- Currie, C. S. M., K. Floyd, B. G. Williams, and C. Dye. 2005. "Cost Affordability and Cost-Effectiveness of Strategies to Control Tuberculosis in Countries with High HIV, Prevalence." *BMC Public Health* 5 (1): 130.

- de Jonghe, E., C. J. Murray, H. J. Chum, D. S. Nyangulu, A. Salomao, and K. Styblo. 1994. "Cost-Effectiveness of Chemotherapy for Sputum Smear-Positive Pulmonary Tuberculosis in Malawi, Mozambique and Tanzania." *International Journal of Health Planning and Management* 9: 151–81.
- de Viedma, D. G., M. Marin, S. Hernangomez, M. Diaz, M. J. R. Serrano, L. Alcalá, and E. Bouza. 2002. "Reinfection Plays a Role in a Population Whose Clinical/Epidemiological Characteristics Do Not Favor Reinfection." *Archives of Internal Medicine* 162: 1873–79.
- Dholakia, R. 1996. *The Potential Economic Benefits of the DOTS Strategy against TB in India*. Geneva: World Health Organization.
- Doherty, T. M., A. Demissie, J. Olobo, D. Wolday, S. Britton, T. Eguale, and others. 2002. "Immune Responses to the *Mycobacterium tuberculosis*-Specific Antigen ESAT-6 Signal Subclinical Infection among Contacts of Tuberculosis Patients." *Journal of Clinical Microbiology* 40 (2): 704–6.
- Dudley, L., V. Azevedo, R. Grant, J. H. Schoeman, L. Dikweni, and D. Maher. 2003. "Evaluation of Community Contribution to Tuberculosis Control in Cape Town, South Africa." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S48–55.
- Dye, C. 2000. "Tuberculosis 2000–2010: Control, but Not Elimination." *International Journal of Tuberculosis and Lung Disease* 4 (Suppl. 2): S146–52.
- Dye, C., and M. A. Espinal. 2001. "Will Tuberculosis Become Resistant to All Antibiotics?" *Proceedings of the Royal Society of London, Series B, Biological Sciences* 268: 45–52.
- Dye, C., G. P. Garnett, K. Sleeman, and B. G. Williams. 1998. "Prospects for Worldwide Tuberculosis Control under the WHO DOTS Strategy." *Lancet* 352: 1886–91.
- Dye, C., S. Scheele, P. Dolin, V. Pathania, and M. C. Raviglione. 1999. "Global Burden of Tuberculosis: Estimated Incidence, Prevalence, and Mortality by Country." *Journal of the American Medical Association* 282: 677–86.
- Dye, C., C. J. Watt, D. M. Bleed, S. M. Hosseini, and M. C. Raviglione. 2005. "The Evolution of Tuberculosis Control, and Prospects for Reducing Incidence, Prevalence and Deaths Globally." *Journal of the American Medical Association* 293: 2767–75.
- Dye, C., C. J. Watt, D. M. Bleed, and B. G. Williams. 2003. "What Is the Limit to Case Detection under the DOTS Strategy for Tuberculosis Control?" *Tuberculosis* 83: 35–43.
- Dye, C., and B. G. Williams. 2000. "Criteria for the Control of Drug-Resistant Tuberculosis." *Proceedings of the National Academy of Sciences USA* 97: 8180–85.
- Dye, C., B. G. Williams, M. A. Espinal, and M. C. Raviglione. 2002. "Erasing the World's Slow Stain: Strategies to Beat Multidrug-Resistant Tuberculosis." *Science* 295: 2042–46.
- Dye, C., F. Zhao, S. Scheele, and B. G. Williams. 2000. "Evaluating the Impact of Tuberculosis Control: Number of Deaths Prevented by Short-Course Chemotherapy in China." *International Journal of Epidemiology* 29: 558–64.
- Espinal, M. A., A. Laszlo, L. Simonsen, F. Boulahbal, S. J. Kim, A. Reniero, and others. 2001. "Global Trends in Resistance to Antituberculosis Drugs." *New England Journal of Medicine* 344: 1294–1303.
- Fine, P. E. M. 2001. "BCG Vaccines and Vaccination." In *Tuberculosis: A Comprehensive International Approach*, ed. L. B. Reichman, and E. S. Hershfield, 503–24. New York: Marcel Dekker.
- Floyd, K. 2003. "Costs and Effectiveness: The Impact of Economic Studies on TB Control." *Tuberculosis (Edinburgh)* 83: 187–200.
- Floyd, K., J. Skeva, T. Nyirenda, F. Gausi, and F. Salaniponi. 2003. "Cost and Cost-Effectiveness of Increased Community and Primary Care Facility Involvement in Tuberculosis Care in Lilongwe District, Malawi." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S29–37.
- Floyd, K., D. Wilkinson, and C. Gilks. 1997. "Comparison of Cost Effectiveness of Directly Observed Treatment (DOT) and Conventionally Delivered Treatment for Tuberculosis: Experience from Rural South Africa." *British Medical Journal* 315 (7): 1407–11.
- Fordham von Reyn, C., and J. M. Vuola. 2002. "New Vaccines for the Prevention of Tuberculosis." *Clinical Infectious Diseases* 35: 465–74.
- Frieden, T. R., P. I. Fujiwara, R. M. Washko, and M. A. Hamburg. 1995. "Tuberculosis in New York City—Turning the Tide." *New England Journal of Medicine* 333: 229–33.
- Frieden, T., T. R. Sterling, S. S. Munsiff, C. J. Watt, and C. Dye. 2003. "Tuberculosis." *Lancet* 362: 887–99.
- Friedland, G., S. Abdool Karim, Q. Abdool Karim, U. Lalloo, C. Jack, N. Gandhi, and W. El Sadr. 2004. "Utility of Tuberculosis Directly Observed Therapy Programs as Sites for Access to and Provision of Antiretroviral Therapy in Resource-Limited Countries." *Clinical Infectious Diseases* 38 (Suppl. 5): S421–28.
- Fruth, U., and D. Young. 2004. "Prospects for New TB Vaccines: Stop TB Working Group on TB Vaccine Development." *International Journal of Tuberculosis and Lung Disease* 8: 151–55.
- Garber, A. M., and C. E. Phelps. 1997. "Economic Foundations of Cost-Effectiveness Analysis." *Journal of Health Economics* 16: 1–31.
- Glynn, J. R., M. D. Yates, A. C. Crampin, B. M. Ngwira, F. D. Mwaungulu, G. F. Black, and others. 2004. "DNA Fingerprint Changes in Tuberculosis: Reinfection, Evolution, or Laboratory Error?" *Journal of Infectious Diseases* 190: 1158–66.
- Goonetilleke, N. P., H. McShane, C. M. Hannan, R. J. Anderson, R. H. Brookes, and A. V. Hill. 2003. "Enhanced Immunogenicity and Protective Efficacy against *Mycobacterium tuberculosis* of Bacilli Calmette-Guérin Vaccine Using Mucosal Administration and Boosting with a Recombinant Modified Vaccinia Virus Ankara." *Journal of Immunology* 171: 1602–9.
- Grange, J. 2003. "Immunophysiology and Immunopathology." In *Clinical Tuberculosis*, 3rd ed., ed. P. D. O. Davies, 88–104. London: Arnold.
- Hamid Salim, M. A., E. Declercq, A. Van Deun, and K. A. R. Saki. 2004. "Gender Differences in Tuberculosis: A Prevalence Survey Done in Bangladesh." *International Journal of Tuberculosis and Lung Disease* 8: 952–57.
- Hernandez-Garduno, E., V. Cook, D. Kunimoto, R. K. Elwood, W. A. Black, and J. M. FitzGerald. 2004. "Transmission of Tuberculosis from Smear Negative Patients: A Molecular Epidemiology Study." *Thorax* 59: 286–90.
- Horwitz, M. A., G. Harth, B. J. Dillon, and S. Maslesa-Galic. 2000. "Recombinant Bacillus Calmette-Guérin (BCG) Vaccines Expressing the *Mycobacterium tuberculosis* 30-kDa Major Secretory Protein Induce Greater Protective Immunity against Tuberculosis Than Conventional BCG Vaccines in a Highly Susceptible Animal Model." *Proceedings of the National Academy of Sciences USA* 97: 13853–58.
- Hudelson, P. 1996. "Gender Differentials in Tuberculosis: The Role of Socio-Economic and Cultural Factors." *Tubercle and Lung Disease* 77: 391–400.
- Jack, W. 2001. "The Public Economics of Tuberculosis Control." *Health Policy* 57: 79–96.
- Jamison, D. T., W. H. Mosley, A. R. Meashem, and J. L. Bobadilla. 1993. *Disease Control Priorities in Developing Countries*. New York: Oxford University Press.
- Johansen, I. S., B. Lundgren, A. Sosnovskaja, and V. Ø. Thomsen. 2003. "Direct Detection of Multidrug-Resistant *Mycobacterium tuberculosis* in Clinical Specimens in Low- and High-Incidence Countries by Line Probe Assay." *Journal of Clinical Microbiology* 41 (9): 4454–56.

- Johnson, J. L., A. Okwera, D. L. Hom, H. Mayanja, C. Mutuluza Kityo, P. Nsubuga, and others. 2001. "Duration of Efficacy of Treatment of Latent Tuberculosis Infection in HIV-Infected Adults." *AIDS* 15: 2137–47.
- Krebs, W. 1930. "Die Fälle von Lungentuberkulose in der aargauischen Heilstätte Barmelweid aus den Jahren 1912–1927." *Beiträge zur Klinik der Tuberkulose* 74: 345–79.
- Kristensen, I., P. Aaby, and H. Jensen. 2000. "Routine Vaccinations and Child Survival: Follow Up Study in Guinea-Bissau, West Africa." *British Medical Journal* 321: 1435–38.
- Letvin, N. L., B. R. Bloom, and S. L. Hoffman. 2001. "Prospects for Vaccines to Protect against AIDS, Tuberculosis, and Malaria." *Journal of the American Medical Association* 285: 606–11.
- Lietman, T., and S. M. Blower. 2000. "Potential Impact of Tuberculosis Vaccines as Epidemic Control Agents." *Clinical Infectious Diseases* 30 (Suppl. 3): S316–22.
- Marais B. J., R. P. Gie, H. S. Schaaf, A. C. Hesselning, C. C. Obihara, L. J. Nelson, and others. 2004. "The Clinical Epidemiology of Childhood Pulmonary Tuberculosis: A Critical Review of Literature from the Pre-Chemotherapy Era." *International Journal of Tuberculosis and Lung Disease* 8: 278–85.
- Marks, G. B., J. Bai, G. J. Stewart, S. E. Simpson, and E. A. Sullivan. 2001. "Effectiveness of Postmigration Screening in Controlling Tuberculosis among Refugees: A Historical Cohort Study, 1984–1998." *American Journal of Public Health* 91: 1797–99.
- McMurray, D. N. 2003. "Recent Progress in the Development and Testing of Vaccines against Human Tuberculosis." *International Journal of Parasitology* 33: 547–54.
- Menzies, D., M. J. Dion, B. Rabinovitch, S. Mannix, P. Brassard, and K. Schwartzman. 2004. "Treatment Completion and Costs of a Randomized Trial of Rifampin for 4 Months versus Isoniazid for 9 Months." *American Journal of Respiratory and Critical Care Medicine* 170: 445–49.
- Moalosi, G., K. Floyd, J. Phatshwane, T. Moeti, N. Binkin, and T. Kenyon. 2003. "Cost-Effectiveness of Home-Based Care versus Hospital Care for Chronically Ill Tuberculosis Patients, Francistown, Botswana." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S80–85.
- Murray, C. J. L., E. de Jonghe, H. J. Chum, D. S. Nyangulu, A. Salomao, and K. Styblo. 1991. "Cost Effectiveness of Chemotherapy for Pulmonary Tuberculosis in Three Sub-Saharan African Countries." *Lancet* 338: 1305–8.
- Murray, C. J. L., and J. A. Salomon. 1998. "Modeling the Impact of Global Tuberculosis Control Strategies." *Proceedings of the National Academy of Sciences USA* 95: 13881–86.
- Mwinga, A., M. Hosp, P. Godfrey-Faussett, M. Quigley, P. Mwaba, B. N. Mugala, and others. 1998. "Twice Weekly Tuberculosis Preventive Therapy in HIV Infection in Zambia." *AIDS* 12: 2447–57.
- Nelson, L. J., and C. D. Wells. 2004. "Global Epidemiology of Childhood Tuberculosis." *International Journal of Tuberculosis and Lung Disease* 8: 636–47.
- Neuenschwander, B. E., M. Zwahlen, S. J. Kim, E. G. Lee, and H. L. Rieder. 2002. "Determination of the Prevalence of Infection with *Mycobacterium tuberculosis* among Persons Vaccinated against *Bacillus Calmette-Guérin* in South Korea." *American Journal of Epidemiology* 155: 654–63.
- Noertjojo, K., C. M. Tam, S. L. Chan, J. Tan, and M. Chan-Yeung. 2002. "Contact Examination for Tuberculosis in Hong Kong Is Useful." *International Journal of Tuberculosis and Lung Disease* 6: 19–24.
- Nyangulu, D. S., A. D. Harries, C. Kang'ombe, A. E. Yadidi, K. Chokani, T. Cullinan, and others. 1997. "Tuberculosis in a Prison Population in Malawi." *Lancet* 350: 1284–87.
- Okello, D., K. Floyd, F. Adatu, R. Odeke, and G. Garglioni. 2003. "Cost and Cost-Effectiveness of Community-Based Care in Rural Uganda." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S72–79.
- Pai, M., L. W. Riley, and J. M. Colford Jr. 2004. "Interferon-gamma Assays in the Immunodiagnosis of Tuberculosis: A Systematic Review." *Lancet Infectious Diseases* 4 (12): 761–76.
- PRC (People's Republic of China) Ministry of Health. 2000. *Report on Nationwide Random Survey for the Epidemiology of Tuberculosis in 2000*. Beijing: PRC Ministry of Health.
- Quigley, M. A., A. Mwinga, M. Hosp, I. Lisse, D. Fuchs, J. D. H. Porter, and P. Godfrey-Faussett. 2001. "Long-Term Effect of Preventive Therapy for Tuberculosis in a Cohort of HIV-Infected Zambian Adults." *AIDS* 15: 215–22.
- Radhakrishna, S., T. R. Frieden, and R. Subramani. 2003. "Association of Initial Tuberculin Sensitivity, Age, and Sex with the Incidence of Tuberculosis in South India: A 15-Year Follow-Up." *International Journal of Tuberculosis and Lung Disease* 7: 1083–91.
- Reed, S. G., M. R. Alderson, W. Dalemans, Y. Lobet, and Y. A. W. Skeiky. 2003. "Prospects for a Better Vaccine against Tuberculosis." *Tuberculosis* 83: 213–19.
- Richardson, M., N. M. Carroll, E. Engelke, G. D. Van Der Spuy, F. Salker, Z. Munch, and others. 2002. "Multiple *Mycobacterium tuberculosis* Strains in Early Cultures from Patients in a High-Incidence Community Setting." *Journal of Clinical Microbiology* 40: 2750–54.
- Rieder, H. L. 1999. "Epidemiologic Basis of Tuberculosis Control." Paris: International Union against Tuberculosis and Lung Disease.
- . 2003. "BCG Vaccines." In *Clinical Tuberculosis*, 3rd ed., ed. P. D. O. Davies, 337–53. London: Arnold.
- Rieder, H. L., D. E. Snider Jr., and G. M. Cauthen. 1990. "Extrapulmonary Tuberculosis in the United States." *American Review of Respiratory Disease* 141: 347–51.
- Shafer, R. W., and B. R. Edlin. 1996. "Tuberculosis in Patients Infected with Human Immunodeficiency Virus: Perspective on the Past Decade." *Clinical Infectious Diseases* 22: 683–704.
- Shilova, M. V., and C. Dye. 2001. "The Resurgence of Tuberculosis in Russia." *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* 356: 1069–75.
- Sinanovic, E., K. Floyd, L. Dudley, V. Azevedo, R. Grant, and D. Maher. 2003. "Cost and Cost-Effectiveness of Community-Based Care for Tuberculosis in Cape Town, South Africa." *International Journal of Tuberculosis and Lung Disease* 7 (Suppl. 1): S56–62.
- Sonnenberg, P., J. R. Glynn, K. Fielding, J. Murray, P. Godfrey-Faussett, and S. Shearer. 2005. "How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners." *Journal of Infectious Diseases* 191: 150–58.
- Styblo, K. 1991. *Epidemiology of Tuberculosis*. 2nd ed. The Hague: Royal Netherlands Tuberculosis Association.
- Suarez, P. G., K. Floyd, J. Portocarrero, E. Alarcon, E. Rapiti, G. Ramos, and others. 2002. "Feasibility and Cost-Effectiveness of Standardised Second-Line Drug Treatment for Chronic Tuberculosis Patients: A National Cohort Study in Peru." *Lancet* 359: 1980–89.
- Suarez, P. G., C. J. Watt, E. Alarcon, J. Portocarrero, D. Zavala, R. Canales, and others. 2001. "The Dynamics of Tuberculosis in Response to 10 Years of Intensive Control Effort in Peru." *Journal of Infectious Diseases* 184: 473–78.
- Sutherland, I. 1968. "The Ten-Year Incidence of Clinical Tuberculosis Following 'Conversion' in 2,550 Individuals Aged 14 to 19 Years." Unpublished progress report of the Tuberculosis Surveillance and Research Unit, KNCV, The Hague, Netherlands.
- . 1976. "Recent Studies in the Epidemiology of Tuberculosis, Based on the Risk of Being Infected with Tubercle Bacilli." *Advances in Tuberculosis Research* 19: 1–63.

- Sutherland, I., E. Svandova, and S. Radhakrishna. 1982. "The Development of Clinical Tuberculosis Following Infection with Tubercle Bacilli: 1. A Theoretical Model for the Development of Clinical Tuberculosis Following Infection, Linking from Data on the Risk of Tuberculosis Infection and the Incidence of Clinical Tuberculosis in the Netherlands." *Tubercle* 63: 255–68.
- Tan-Torres Edejer, T., R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D. B. Evans, and C. J. L. Murray, eds. 2004. *WHO Guide to Cost-Effectiveness Analysis*. Geneva: World Health Organization.
- Terris-Prestholt, F., and L. Kumaranayake. 2003. "Cost Analysis of the Zambian ProTEST Project: A Package to Reduce the Impact of Tuberculosis and Other HIV-Related Diseases." Unpublished report, London School of Hygiene and Tropical Medicine.
- Toman, K. 1979. *Tuberculosis Case-Finding and Chemotherapy. Questions and Answers*. Geneva: World Health Organization.
- Uplekar, M., V. Pathania, and M. Raviglione. 2001. "Private Practitioners and Public Health: Weak Links in Tuberculosis Control." *Lancet* 358: 912–16.
- van Rie, A., R. Warren, M. Richardson, T. C. Victor, R. P. Gie, D. A. Enarson, and others. 1999. "Exogenous Reinfection as a Cause of Recurrent Tuberculosis after Curative Treatment." *New England Journal of Medicine* 341: 1174–79.
- Vassall, A., S. Bagdadi, H. Bashour, H. Zaher, and P. V. Maaren. 2002. "Cost-Effectiveness of Different Treatment Strategies for Tuberculosis in Egypt and Syria." *International Journal of Tuberculosis and Lung Disease* 6: 1083–90.
- Verver, S., R. M. Warren, Z. Munch, E. Vynnycky, P. D. van Helden, M. Richardson, and others. 2004. "Transmission of Tuberculosis in a High Incidence Urban Community in South Africa." *International Journal of Epidemiology* 33: 351–57.
- Vynnycky, E., and P. E. M. Fine. 1997. "The Natural History of Tuberculosis: The Implications of Age-Dependent Risks of Disease and the Role of Reinfection." *Epidemiology and Infection* 119: 183–201.
- . 2000. "Life Time Risks, Incubation Period, and Serial Interval of Tuberculosis." *American Journal of Epidemiology* 152: 247–63.
- Whalen, C. C., J. L. Johnson, A. Okwera, D. L. Hom, R. Huebner, P. Mugenyi, and others. 1997. "A Trial of Three Regimens to Prevent Tuberculosis in Ugandan Adults Infected with the Human Immunodeficiency Virus." *New England Journal of Medicine* 337: 801–8.
- WHO (World Health Organization). 2001. *Vaccine Preventable Diseases: Monitoring System—2001 Global Summary*. Geneva: WHO, Department of Vaccines and Biologicals.
- . 2002a. *An Expanded DOTS Framework for Effective Tuberculosis Control*. Geneva: WHO.
- . 2002b. *The World Health Report: Reducing Risks, Promoting Healthy Life*. Geneva: WHO.
- . 2004a. *Anti-Tuberculosis Drug Resistance in the World*. Report 3. Geneva: WHO.
- . 2004b. *Cost and Cost-Effectiveness of Public-Private Mix DOTS: Evidence from Two Pilot Projects in India*. Geneva: WHO.
- . 2004c. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva: WHO.
- . 2004d. *Public-Private Mix for DOTS: Global Progress*. Geneva: WHO.
- . 2004e. *Respiratory Care in Primary Care Services—A Survey in 9 Countries*. Geneva: WHO.
- . 2004f. *World Health Report 2004: Changing History*. Geneva: WHO.
- . 2005. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva: WHO.
- Wilkinson, D., K. Floyd, and C. F. Gilks. 1997. "Costs and Cost-Effectiveness of Alternative Tuberculosis Management Strategies in South Africa—Implications for Policy." *South African Medical Journal* 87 (4): 451–55.
- Wilkinson, D., S. B. Squire, and P. Garner. 1998. "Effect of Preventive Treatment for Tuberculosis in Adults Infected with HIV: Systematic Review of Randomised Placebo Controlled Trials." *British Medical Journal* 317: 625–29.
- Williams, B. G., and C. Dye. 2003. "Antiretroviral Drugs for Tuberculosis Control in the Era of HIV/AIDS." *Science* 301: 1535–37.
- Woods, G. L. 2001. "Molecular Techniques in Mycobacterial Detection." *Archives of Pathology and Laboratory Medicine* 125 (1): 122–26.
- Young, D. B., and G. R. Stewart. 2002. "Tuberculosis Vaccines." *British Medical Bulletin* 62: 73–86.



## Chapter 18

# HIV/AIDS Prevention and Treatment



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Although global commitment to control the HIV/AIDS pandemic has increased significantly in recent years, the virus continues to spread with alarming and increasing speed. By the end of 2005, an estimated 40 million people worldwide were living with HIV infection or disease, a notable rise from the 35 million infected with HIV in 2001 (UNAIDS 2005). In 2005, close to 5 million new HIV infections and 3 million AIDS deaths occurred, more of both than in any previous year. Sub-Saharan Africa remains the region most affected by HIV/AIDS; however, the virus is now spreading rapidly in Asia and parts of Eastern Europe.

Despite the rapid spread of HIV, several countries have achieved important success in curbing its transmission. The extraordinary potential of HIV prevention is exemplified by such diverse efforts as Thailand's 100 percent condom program, Uganda's remarkable decrease in HIV prevalence, and the community-based syndromic management of sexually transmitted infections (STIs) in Mwanza, Tanzania. Box 18.1 describes characteristics common to these programs.

Successes also include the development and effective use of highly sensitive and specific HIV screening tests, which have virtually eliminated infection from the blood supply in the developed world and in most parts of the developing world (WHO 2002a). In addition, the administration of a short course of nevirapine to mothers during labor and to newborns postpartum reduces the risk of mother-to-child transmission (MTCT) by as much as 47 percent (Guay and others 1999). However, recent data suggest that such short-term successes may be at the expense of resistance and viral failure once treatment is introduced after delivery (Eshleman and others 2001).

Enormous advances in HIV/AIDS treatment regimens have fundamentally altered the natural history of the disease and sharply reduced HIV-related morbidity and mortality in countries where such treatments are accessible. The advent of antiretroviral drugs in the late 1980s began a revolution in the management of HIV, which can be seen as analogous to the use of penicillin for treating bacterial infections in the 1940s. The most notable advance on the treatment front is the use of combination antiretroviral therapy, which is far more effective than monotherapy (zidovudine or AZT), the standard of care when the first edition of this volume was published. Recent declines in the price of combination antiretroviral therapy in developing countries from US\$15,000 per year to less than US\$150 in some countries have prompted numerous developing countries to introduce antiretroviral therapy through the public sector. These declines also pose difficult questions regarding the optimal allocation of limited resources for HIV/AIDS, as well as the potential impact on already strained health care infrastructures.

### OBSTACLES TO HIV CONTROL

Obstacles to effective HIV control include lack of prevention and care coverage and lack of rigorous evaluations. Both are discussed below.

#### Lack of Coverage and Access to Prevention Services

Notwithstanding these treatment strides, global efforts have not proved sufficient to control the spread of the pandemic or to extend the lives of the majority of those infected. The desired level of success has not yet been achieved for several reasons.

## Box 18.1

### Successful HIV Prevention Strategies

The HIV prevention success stories highlighted in this chapter stem in part from each country's unique cultural, historical, and infrastructural elements. Nevertheless, these successes share several common features, thereby offering potential guidance for the development and implementation of prevention strategies in other settings. These features include:

- high-level political leadership
- active engagement of civil society and religious leaders in a multisectoral approach

Source: Authors.

- population-based programs designed to change social norms
- increased open communication about sexual activities and HIV/AIDS
- programs to combat stigma and discrimination
- condom promotion
- STI surveillance and control
- interventions targeting key “bridge” populations—populations that transmit the virus from high-risk to low-risk groups.

Most people who could benefit from available control strategies, including treatment, do not have access to them. Modelers commissioned by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) determined that existing interventions could prevent 63 percent of all infections projected to occur between 2002 and 2010 (Stover and others 2002). Nonetheless, a 2003 survey of coverage revealed that fewer than one in five people at high risk of infection had access to the most basic prevention services, including condoms, AIDS education, MTCT prevention, voluntary counseling and testing (VCT), and harm reduction programs (Global HIV Prevention Working Group 2003). WHO and UNAIDS estimate that only about 7 percent of the nearly 6 million people in need of treatment receive it and that the number of people who require antiretroviral therapy increases by 8,000 each day (UNAIDS 2004).

Current coverage shortfalls, combined with the relentless expansion of the epidemic, underscore the acute need for rapid scale-up of prevention and treatment interventions—an imperative that the international community has acknowledged but that remains to be realized after more than 15 years. However, the activities of the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the U.S. President's Emergency Plan for AIDS Relief (a five-year, US\$15 billion initiative) suggest a growing commitment to tackle these issues. The latter aims to provide antiretroviral drugs for 2 million HIV-infected people, to prevent 7 million new infections, to provide care for 10 million individuals, and to develop health system capacity in Vietnam and in Africa and the Caribbean. Even though 15 countries are currently slated to receive support from the President's Emergency Plan, many of the countries most affected by HIV/AIDS—including Lesotho, Malawi, Swaziland, and Zimbabwe—are not included in the list of beneficiary countries.

Because antiretroviral therapy has historically been unavailable in most developing countries, national programs have lacked the means to undertake a comprehensive approach to HIV/AIDS (notable exceptions are Argentina, Brazil, and Mexico, which provide universal coverage for antiretroviral therapy). As discussed in chapter 8, control of the pandemic demands a two-front battle that emphasizes both prevention and care. Even though the prospect of greater access to treatment increases the feasibility of integrating prevention and care in resource-limited settings, it also raises new questions regarding the selection of optimal prevention programs to pair with treatment programs.

### Lack of Rigorous Evaluations

In addition to poor coverage of key interventions, perhaps the greatest challenge to effective global control is the lack of reliable evidence to guide the selection of interventions for specific areas or populations. In the same way that global policy makers are increasingly recognizing the need for rigorous evaluation of development programs to ensure their success and eliminate waste, the need for reliable scientific evaluations of AIDS control programs is equally paramount for the same reasons. There are simply not enough resources to do everything everywhere; choices must be made and priorities set. In the HIV/AIDS field, this information deficit is especially pronounced with respect to HIV prevention in general and prevention implemented on a population level in particular. Currently, the allocation of resources for HIV/AIDS prevention is seldom evidence based, primarily because of a lack of data on both the effectiveness and the cost of interventions (Feachem 2004).

Few evaluations have collected data specifically on HIV infection as an outcome (Fleming and DeMets 1996). In the

case of care and treatment, success and failure are more readily and rapidly apparent, leading to a substantial degree of auto-correction of ineffective policies. In contrast, with respect to HIV prevention, it is unlikely that those infections that might have occurred in the absence of a prevention program would be monitored, thus reducing the meaningfulness of the auto-feedback cycle for prevention. This underscores the importance of proactive, rigorous evaluation to differentiate success from failure in a timely manner. Sound evidence on the effectiveness of HIV prevention measures is especially important in light of the tendency of many governments and international aid agencies to avoid programs that address sexual behaviors, drug use, and highly stigmatized and vulnerable populations.

In addition, prevention studies have rarely incorporated the well-defined control or comparison groups necessary to identify contextual factors that are essential for appropriately tailoring interventions to the diverse regional settings and the myriad of microenvironments in which HIV transmission occurs (Grassly and others 2001). Contextual data are similarly critical for developing strategies to combat HIV/AIDS-related stigma and restrictive social and gender norms, which often frustrate attempts to address sexual and addictive behaviors associated with HIV transmission. Even where national efforts have succeeded in curbing the spread of the epidemic, as in Senegal and Uganda, evidence often does not clearly indicate the specific, well-defined, contextual features that account for success.

The lack of both contextual data and sound evidence regarding the effectiveness of HIV interventions hinders policy makers' ability to tailor HIV interventions to the nature and stage of national epidemics, something that the authors argue is necessary to address HIV/AIDS effectively. In the absence of such data, HIV/AIDS expenditures undoubtedly incorporate an unacceptable degree of waste, people are unnecessarily becoming infected with HIV, and HIV-infected individuals are dying prematurely.

Why has this type of research not been more forthcoming? In part it is because, by definition, such research is less innovative scientifically and also typically less experimental than research to develop new interventions. It is handicapped both in competing for traditional research funding and in receiving academic recognition. The only way to redress the imbalance is through specific earmarking of significant research funds.

## ACTION UNDER UNCERTAINTY

Even though the current deficit in evaluation research is glaring, the magnitude and seriousness of the global pandemic means that action is nevertheless required. Moreover, despite such gaps in knowledge, we can still improve control strategies by tailoring interventions to the nature and scope of the epidemic. Summarized below is what is known with regard to the

burden of disease, the determinants of transmission, and the effectiveness and cost-effectiveness of existing prevention interventions.

### Burden of Disease

As a result of large-scale implementation of data collection methods for surveillance worldwide and enhanced methods for validating and interpreting HIV-related data, the HIV/AIDS epidemic is probably one of the best documented epidemics in history. An increasing number of data sources contribute to reasonably accurate estimates and a more nuanced understanding of the epidemic's trends. Unfortunately, this relatively accurate picture of where the epidemic is and has been is not matched by similarly convincing maps of the factors that explain its spread.

Although no single country has been spared the virus, the epidemic has affected certain regions of the world disproportionately, and Sub-Saharan Africa remains by far the hardest hit region (table 18.1). With only 10 percent of the world's population, it accounts for more than 75 percent of all HIV infections worldwide and more than 75 percent of AIDS-related deaths estimated for 2003. Asia and the Pacific, with several large and populous countries, account for 7.4 million infections, or 19.5 percent of the current burden of disease. Prevention and treatment efforts in Sub-Saharan Africa and Asia—regions that together represent 85 percent of all current infections—have dictated, and will continue to dictate, global trends in the burden of HIV- and AIDS-related mortality.

Between 1997 and 2001, the percentage of women living with HIV/AIDS increased from 41 to 50 percent. This trend is most apparent in Sub-Saharan Africa, where women represent 57 percent of adults living with HIV and 75 percent of HIV-infected young people. Even though women account for a smaller share of infections in Asia (28 percent), the disease burden among women and girls is likely to rise as the epidemic becomes generalized. More detailed information about the global burden of HIV/AIDS, regional differences, and trends over time is available in the UNAIDS (2005) report on the global AIDS epidemic.

### Determinants of Infection

HIV transmission predominantly occurs through three mechanisms: sexual transmission, exposure to infected blood or blood products, or perinatal transmission (including breastfeeding). The likelihood of transmission is heavily affected by social, cultural, and environmental factors that often differ markedly between and within regions and countries. There is also some indication that molecular, viral, immunological, or other host factors might influence the likelihood of HIV transmission. For a more detailed discussion of sexual behaviors and the contextual determinants of infection, see chapter 17.

**Table 18.1** Deaths and Disability-Adjusted Life Years Attributed to AIDS by Region, Age, and Gender, 2001

Region	Number (thousands)			Percentage female
	Total	Both sexes, age 0–14	Both sexes, age 15+	
<i>Deaths</i>				
World	2,576	439	2,133	46
High-income countries	22	0	21	23
Low- and middle-income countries	2,554	439	2,111	46
Sub-Saharan Africa	2,058	408	1,651	51
East Asia and the Pacific	107	5	100	25
Europe and Central Asia	28	0	27	14
Latin America and the Caribbean	83	8	73	36
Middle East and North Africa	4	0	2	25
Southeast Asia	272	18	255	23
<i>Disability-adjusted life years</i>				
World	71,460	13,586	57,875	47
High-income countries	665	7	660	23
Low- and middle-income countries	70,795	13,579	57,215	47
Sub-Saharan Africa	56,820	12,526	44,294	52
East Asia and the Pacific	3,121	195	2,927	25
Europe and Central Asia	982	25	957	18
Latin America and the Caribbean	2,354	260	2,092	36
Middle East and North Africa	105	20	84	39
Southeast Asia	7,413	553	6,861	25

Source: Mathers and others 2006.

**Table 18.2** Estimated HIV Transmission Risk per Exposure

Type of exposure	Estimated risk HIV transmission per exposure
Receptive anal intercourse	≤ 3.0 percent (1/125 to 1/31) (DeGruttola and others 1989)
Receptive vaginal intercourse	≤ 0.1 percent (1/2,000 to 1/667) (Mastro and others 1994; Wiley, Herschkorn, and Padian 1989)
Insertive vaginal or anal intercourse	≤ 0.1 percent (1/3,333 to 1/1,111) (Nagachinta and others 1997; Peterman and others 1988)
Needlestick injury	= 0.3 percent (1/313) (Henderson and others 1990)
Use of contaminated injecting drug equipment	= 0.6 percent (1/149) (Kaplan and Heimer 1992)
Mucous membrane	= 0.1 percent (1/1,111) (Ippolito, Puro, and De Carli 1993)

Source: Authors.

**Sexual Transmission.** Worldwide, sexual intercourse is the predominant mode of transmission, accounting for approximately 80 percent of infections (Askew and Berer 2003). Sexual intercourse accounts for more than 90 percent of infections in Sub-Saharan Africa. Although many people who know they are infected reduce their risk behaviors, studies in developed countries suggest that a substantial percentage nevertheless continue to engage in unprotected sex (Marks, Burris, and Peterman 1999). The risk of sexual transmission is determined by behaviors that influence the likelihood of exposure to an

infected individual and by infectivity in the event of exposure. This also includes factors related to the infectiousness of the infected partner and the susceptibility of the uninfected partner.

**Infectivity** The per contact infectivity of HIV from sexual transmission varies depending on sexual activity (Royce and others 1997). Anal intercourse carries a higher transmission probability than penile-vaginal intercourse, and male-to-female transmission is more likely than female-to-male transmission. Data on infectivity by transmission mode are shown in table 18.2.

**Biological Mediators of Infectivity** Untreated STIs increase the risk of sexual HIV transmission several-fold (Institute of Medicine 1997). Numerous epidemiological studies have supported the association of genital ulcers in general and of genital herpes (herpes simplex virus 2, or HSV-2) in particular with HIV infection (Hook and others 1992). Not only does the biological interaction between HSV-2 and HIV enhance the transmission and acquisition of HIV, but HIV infection is also associated with more frequent reactivation of HSV-2. The presence of herpetic ulcers and lesions allows an entry point for HIV in the uninfected individual, and the presence of high copy numbers of HIV ribonucleic acid (RNA) in HSV-2 lesions in HIV-infected individuals underscores the importance for HIV prevention of controlling HSV-2 infections (Mbopi Keou and others 1999).

Vaginal infections are also emerging as important risk factors for HIV. For example, infection with trichomonas increases the risk for HIV seroconversion (Buve 2002). In addition, higher trichomonas rates have been detected in regions of Sub-Saharan Africa that have higher HIV rates, and investigators working throughout Sub-Saharan Africa report similar results, with odds ratios from 1.5 to 56.8 (Gregson and others 2001). In addition, studies have shown an increased risk of HIV acquisition in patients who have bacterial vaginosis (Martin and others 1999).

Circumcision also affects HIV transmission. In a meta-analysis of 27 studies (Weiss, Quigley, and Hayes 2000), uncircumcised men were almost twice as likely to be infected with HIV as those who were circumcised. Studies that controlled adequately for other risks and studies that separately assessed risk in high-risk populations, such as STI clinic attendees or truck drivers, found an even stronger protective effect of circumcision. Similarly, an ecological study comparing two high-prevalence Sub-Saharan African cities with two low-prevalence cities found that circumcised individuals were substantially less likely to be infected with HIV (Avert and others 2001). Two recent studies conducted in Kenya and India (Donnelly 2004; Reynolds and others 2004) found that uncircumcised men had an HIV rate 7 to 11 times greater than circumcised men. More recently, results from a randomized controlled trial conducted in South Africa indicated that the risk of HIV acquisition was reduced by more than 60 percent of men randomized for circumcision (controlling for sexual behavior, including condom use and health seeking behavior) in a community where more than 30 percent of the women were infected (Avert and others 2005).

Before circumcision among adult males becomes a widespread policy recommendation, results are still pending in two similar trials. Obviously one issue is the acceptability of such a procedure as well as the fact that some increase in high risk sexual activity was noted among the men who were circumcised, although this did not offset the results of the intervention.

The risk of sexual transmission is also strongly correlated with the plasma level of virus in the infected individual (Quinn and others 2000); thus, infectivity varies over the natural progression of the disease. Individuals are most infectious subsequent to infection and again during the late stage of the disease. Antiretroviral therapy significantly reduces the level of virus, often to the point that standard tests cannot detect HIV in the patient's blood (Palella and others 1998). Available data suggest that viral load reductions induced by antiretroviral therapy will lower infectiousness. Studies have shown a close relationship between the amount of viral suppression and the risk of vertical transmission (Garcia and others 1999). Quinn and others (2002) show that the risk of sexual transmission between couples in Africa was strongly related to the level of viral load in the infected partner.

**Exposure to Infected Blood or Blood Products.** Injection drug use and blood transfusion are two mechanisms of HIV exposure to infected blood. Determinants of each are discussed below.

**Injection** Because of the efficiency of HIV transmission through needle sharing, the introduction of HIV into an urban network of injecting drugs users can quickly lead to extraordinarily high HIV prevalence in this population. Sharing of injection equipment and frequency of injection are both important correlates of HIV infection (Chaisson and others 1989). Attendance at shooting galleries, where sharing with anonymous injecting partners is likely to occur, is also an independent risk factor across many studies (Vlahov and others 1990). Injecting cocaine (associated with "booting" or "kicking," where blood is drawn into the syringe and then injected) and having a number of needle-sharing partners are also associated with HIV infection (Anthony and others 1991).

**Blood Transfusion** The probability of becoming infected through an HIV-contaminated transfusion is estimated at more than 90 percent (UNAIDS 1997), and the amount of HIV in a single contaminated blood transfusion is so large that individuals infected in this manner may rapidly develop AIDS. Currently, between 5 and 10 percent of HIV infections worldwide are transmitted through the transfusion of contaminated blood products (WHO 2002a). Setting up and maintaining a safe blood supply will virtually eliminate HIV transmission through transfusions.

**Perinatal Transmission.** Perinatal HIV transmission includes both vertical transmission and transmission during breastfeeding. Determinants of each are discussed below.

**Vertical Transmission** Perhaps the most compelling evidence of the significance of viral load and transmission risk has been

documented with respect to MTCT. Maternal viral load, as quantified by RNA polymerase chain reaction, is associated with increased risk in each mode of vertical transmission. A recent randomized clinical trial in Kenya found that maternal plasma HIV RNA levels higher than 43,000 copies per milliliter were associated with a fourfold increase in vertical transmission (John and others 2001).

Independent of HIV RNA levels in maternal plasma, additional risk factors include cervical HIV deoxyribonucleic acid (DNA), vaginal HIV DNA, and cervical or vaginal ulcers. Chorioamnionitis has also been documented as a risk factor for MTCT among African mothers (Ladner and others 1998), as has exposure to maternal blood during labor and delivery. Newell (2003) estimates that for every hour an infant is exposed to ruptured membranes, the risk of transmission increases by 2 percent.

**Breastfeeding** Transmission through breastfeeding is likely associated with an elevated viral load in the breast milk, which in turn is associated with maternal plasma viral load and CD4 T cell levels. Mastitis has also been associated with increased risk of vertical transmission. Meta-analyses suggest that the cumulative probability of HIV infection increases from 0.6 percent at age 6 months to 9.2 percent at age 3 (Read 2003). A study in Malawi, however, indicates that most transmission occurs in the early breastfeeding months, with an incidence per month of 0.7 percent at age 1 to 5 months, 0.6 percent at age 6 to 11 months, and 0.3 percent at age 12 to 17 months (Miotti and others 1999). In one study, infants who were breastfed in combination with receiving other supplementary foods were twice as likely to be infected at age 6 months than infants fed exclusively on breast milk or on formula (Coutsoudis and others 2001). The hypothesis is that antigens and bacterial contaminants present in supplemental fluids and foods consumed by infants who are not exclusively breastfed may cause inflammation and microtrauma to the infant's intestinal gut, thereby facilitating viral transmission. Another hypothesis is that mixed feeding increases the risk of subclinical or clinical mastitis in the mother, which could increase milk viral load (Semba and others 1999).

Decisions about breastfeeding are further complicated by recent data indicating possible increased mortality among breastfeeding mothers (Nduati and others 2001) and by the stigma associated with not breastfeeding in countries where abstaining from breastfeeding is tantamount to disclosing a woman's HIV status.

### **Effectiveness and Cost-Effectiveness of Prevention Interventions**

Below we discuss the need for ongoing surveillance and contextual data to determine the effectiveness of HIV interventions

and how best to implement those interventions. We then discuss the existing effectiveness and cost-effectiveness data.

**Essential Background Data for Any Intervention.** Because the prioritization of prevention strategies for any epidemic requires accurately identifying the epidemiological profile (discussed below), maintaining a sound and reliable public health surveillance system is a prerequisite for an effective prevention response. An understanding of HIV and STI prevalence and trends, as well as the prevalence and distribution of behaviors that contribute to the epidemic's spread, should be supplemented by national monitoring systems that track sources and uses of funding to promote greater accountability. In addition, data are needed to identify and characterize key contextual issues that affect the selection of interventions.

Although surveillance is essential for an optimally strategic public health response, its utility depends on the degree to which the information it yields is effectively deployed. As noted below, countries with concentrated epidemics should prioritize interventions that are targeted to the populations at highest risk. In Latin America, however, where information on national AIDS funding is strongest, the proportion of limited prevention resources that is not targeted to the populations at highest risk of infection varies from less than 5 percent to more than 50 percent (Saavedra 2000). This range strongly suggests that resource allocation is frequently not based on available epidemiological and effectiveness data.

Table 18.3 summarizes information about the effectiveness of the interventions discussed below.

**Cost-Effectiveness Estimates for Prevention Interventions.** How countries spend funds and which interventions they prioritize should be guided by estimates of the relative cost-effectiveness of such interventions. Unfortunately, reliable estimates of cost-effectiveness are largely lacking, for a number of reasons. The main reason is that HIV prevention interventions are difficult to force into a typology that clearly distinguishes one intervention from another. For example, the counseling component of VCT has a strong information-sharing element that overlaps with (a) information, education, and communication (IEC) through the media; (b) peer interventions; and (c) the counseling component of STI treatment. Similarly, the psychological support offered through counseling is comparable to support provided through support groups or to interventions designed to increase social support. Such overlap and duplication among components of different interventions complicate efforts to estimate both the effectiveness and the cost-effectiveness of different interventions.

Several authors have recently reviewed estimates of cost-effectiveness for the prevention interventions described here (Creese and others 2002; Jha and others 2001; Marseille and others 2002; Walker 2003). These reviews address a number of

**Table 18.3** Effectiveness of HIV Interventions

Intervention	Outcome	Effect	Citations
School-based education	Sexual debut	The number of students reporting early sexual debut was significantly lower in the intervention group in both studies.	Hayes and others 2003; Stanton and others 1998
	Multiple sex partners	The number of students reporting multiple sex partners was significantly lower in the intervention group in both studies.	Fawole and others 1999; Hayes and others 2003
	Condom use	Condom use was significantly higher in the intervention group in three of the four studies and nonsignificantly higher in one study.	Fawole and others 1999; Harvey, Stuart, and Swan 2000; Hayes and others 2003; Stanton and others 1998
	HIV incidence	The study found no significant differences in HIV incidence.	Hayes and others 2003
	STI prevalence and incidence	The study found no significant differences in STI prevalence and incidence.	Hayes and others 2003
Abstinence education	Condom use	The study found no significant differences in condom use.	Jemmott, Jemmott, and Fong 1998
	Early sexual debut	The study found no significant differences in early sexual debut.	Meekers 2000
VCT <sup>a</sup>	Condom use	Condom use was significantly higher in the intervention group in six of the seven studies and unchanged in one study.	Bentley and others 1998; Bhave and others 1995; Deschamps and others 1996; Jackson and others 1997; Kamenga and others 1991; Levine and others 1998; Voluntary HIV-1 Counseling and Testing Efficacy Study Group 2000
	Unprotected intercourse	Unprotected intercourse was significantly lower in the intervention group in both studies.	Deschamps and others 1996; Voluntary HIV-1 Counseling and Testing Efficacy Study Group 2000
	HIV incidence	HIV incidence was significantly lower in the intervention group in one of the studies and nonsignificantly lower in the other study.	Bhave and others 1995; Celentano and others 2000
Peer-based programs	STI prevalence and incidence	STI prevalence and incidence were significantly lower in the intervention group in all three studies.	Celentano and others 2000; Jackson and others 1997; Levine and others 1998
	Condom use	Condom use was significantly higher in the intervention group in all four studies.	Kelly and others 1997; Norr and others 2004; Sikkema and others 2000; Stanton and others 1996
	Unprotected intercourse	Unprotected intercourse was significantly lower in the intervention group in all four studies.	Basu and others 2004; Kegeles, Hays, and Coates 1996; Kelly and others 1997; Sikkema and others 2000
Peer-based programs	Communication about condoms with partner	Communication was significantly higher in the intervention group.	Lauby and others 2000
	HIV incidence	HIV incidence was significantly lower in the intervention group in both studies.	Ghys and others 2002; Katzenstein and others 1998
	STI prevalence and incidence	STI prevalence and incidence were significantly lower in the intervention group.	Ghys and others 2002
Condom promotion and distribution and IEC <sup>a</sup>	Condom use	Condom use was significantly higher in the intervention group in 10 of the 11 studies and unchanged in 1 study.	Bentley and others 1998; Bhave and others 1995; Egger and others 2000; Ford and others 1996; Jackson and others 1997; Jemmott, Jemmott, and Fong 1998; Kagimu and others 1998; Laga and others 1994; Levine and others 1998; Ngugi and others 1988; Pauw and others 1996

*(Continues on the following page.)*

**Table 18.3. Continued**

Intervention	Outcome	Effect	Citations
	HIV incidence	HIV incidence was significantly lower in the intervention group in two out of three studies and nonsignificantly lower in one study.	Bhave and others 1995; Celentano and others 2000; Laga and others 1994
	STI prevalence and incidence	STI prevalence and incidence were significantly lower in the intervention group in all four studies.	Bhave and others 1995; Celentano and others 2000; Jackson and others 1997; Laga and others 1994; Levine and others 1998
Condom social marketing	Condom use	Condom use was significantly higher in the intervention group in one study; no significant differences were found in the other study.	Agha, Karlyn, and Meekers 2001; Meekers 2000
	Early sexual debut	The study found no significant differences in early sexual debut.	Meekers 2000
STI treatment <sup>a</sup>	HIV incidence	HIV incidence was significantly lower in the intervention group in two of the studies, but the other two studies found no significant differences.	Grosskurth and others 1995; Kamali and others 2003; Laga and others 1994; Wawer and others 1999
	STI prevalence and incidence	The prevalence and incidence of STIs were significantly lower in the intervention group in all six studies.	Jackson and others 1997; Kamali and others 2003; Laga and others 1994; Mayaud and others 1997; Wawer and others 1999
Antiretroviral therapy to reduce MTCT	Mother-to-infant transmission <sup>b</sup>	Significant reduction in mother-to-infant HIV transmission in the intervention group was found in all eight studies, with a range of 33 to 67 percent reduction in transmission.	Ayoubu and others 2003; Connor and others 1994; Dabis and others 1999; Guay and others 1999; Jackson and others 2003; PETRA Study Team 2002; Shaffer and others 1999; Wiktor and others 1999
MTCT feeding substitutions	Mother-to-infant transmission	Use of breast milk substitutes prevented 44 percent of infant infections and was associated with significantly improved HIV-1-free survival.	Nduati and others 2000
Harm reduction in injecting drug users	HIV incidence	Significant reduction in HIV incidence in the intervention group was found in both studies.	Des Jarlais and Friedman 1996; Hurley, Jolley, and Kaldor 1997
	Reuse or sharing of syringes	Significant reduction in needle sharing in the intervention group was found in all three studies; correlation between needle exchange program attendance and lower needle sharing was found in one study.	Jenkins and others 2001; Ksobiech 2003; Peak and others 1995; Vlahov and others 1997
Drug substitution for injecting drug users	Drug use	This meta-analysis found significantly lower rates of drug use.	Metzger, Navaline, and Woody 1998
Blood safety	HIV infections averted	HIV screening was associated with a reduction in HIV infections by both studies.	Foster and Buve 1995; Laleman and others 1992
	Units of HIV-positive blood averted	HIV screening was associated with a reduction in units of HIV-positive blood.	Jacobs and Mercer 1999
Universal precautions	Blood volume transferred in needlestick injury	Glove material reduced the transferred blood volume by 46 to 86 percent.	Mast, Woolwine, and Gerberding 1993
Antiretroviral therapy for prevention, postexposure prophylaxis	HIV seroconversion	The study found a significant relationship between seroconversion and not having received antiretroviral therapy.	Cardo and others 1997
Behavior change for those HIV positive	Condom use	Condom use was significantly higher in the intervention group.	Kalichman and others 2001
	Unprotected intercourse	Unprotected intercourse was significantly lower in the intervention group.	Kalichman and others 2001

Source: Authors.

a. Studies examined may have included educational components, condom promotion and distribution components, HIV testing and counseling, or STI treatment.

b. The types of MTCT antiretroviral therapy varied in these studies.

**Table 18.4** Cost-Effectiveness of Interventions by Epidemic Profile

Intervention	Epidemic profile (2001 US\$)				UNAIDS estimate of need for 2007	
	Low-level epidemic (Middle East and North Africa)	Concentrated epidemic (East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, South Asia)	Generalized low-level epidemic (Sub-Saharan Africa)	Generalized high-level epidemic (Sub-Saharan Africa)	2003 US\$ millions	Percentage of all prevention needs
Surveillance	No CE studies found	No CE studies found	No CE studies found	No CE studies found	—	—
IEC	No CE studies found	No CE studies found	No CE studies found	No CE studies found	129	1
School-based education	No CE studies found	India (E/D/no STIs) US\$1,350 per HIV infection US\$68 per DALY (World Bank 1999)	No CE studies found	No CE studies found	100	1
Abstinence education	No CE studies found	No CE studies found	No CE studies found	No CE studies found	—	—
VCT	No CE studies found	India US\$196 per HIV infection US\$10 per DALY (World Bank 1999)	Chad (M/S/no STIs) US\$891 to US\$5,213 per HIV infection US\$45 to US\$261 per DALY (Hutton, Wyss, and N'Diekhhor 2003) Kenya and Tanzania (M/S/STI) US\$270 to US\$376 per HIV infection US\$14 to US\$19 per DALY (Sweat and others 2000)	No CE studies found	2,175	22

(Continues on the following page.)

**Table 18.4** Continued

Intervention	Epidemic profile (2001 US\$)			UNAIDS estimate of need for 2007		
	Low-level epidemic (Middle East and North Africa)	Concentrated epidemic (East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, South Asia)	Generalized low-level epidemic (Sub-Saharan Africa)	Generalized high-level epidemic (Sub-Saharan Africa)	Percentage of all prevention needs	
Peer-based programs	No CE studies found	United States (E/S/no STIs) US\$71,113 per HIV infection, US\$3,556 per DALY (Pinkerton and others 1998) United States (E/D/no STIs) US\$14,934 to US\$18,719 per HIV infection US\$747 to US\$936 per DALY (Kahn and others 2001) India (sex workers) US\$52 per HIV infection US\$3 per DALY (World Bank 1999) India (high-risk men) US\$303 per HIV infection US\$15 per DALY (World Bank 1999)	Chad (sex workers) US\$6 to US\$30 per HIV infection US\$0 to US\$2 per DALY (Hutton, Wyss, and N'Diekhor 2003) Chad (high-risk men) US\$24 to US\$1,476 per HIV infection US\$1 to US\$74 per DALY (Hutton, Wyss, and N'Diekhor 2003) Chad (youths) US\$129 to infinity per HIV infection US\$6 to infinity per DALY (Hutton, Wyss, and N'Diekhor 2003) Cameroon (E/D/STIs) US\$67 to US\$137 per HIV infection US\$3 to US\$7 per DALY (Kumaranyake and others 1998)	No CE studies found	3,696	37
Condom promotion and distribution and IEC	No CE studies found	No CE studies found	No CE studies found	South Africa (female condom) (M/D/STI) US\$378 to US\$4,094 per HIV infection US\$19 to US\$205 per DALY (Marseille and others 2001)	1,093	11

Condom social marketing	No CE studies found	Chad US\$77 per HIV infection US\$4 per DALY (Hutton, Wyss, and N'Diekhor 2003)	No CE studies found	198	2
STI treatment	No CE studies found	Chad US\$1,675 per HIV infection US\$84 per DALY (Hutton, Wyss, and N'Diekhor 2003) Tanzania (E/S/STI) US\$326 per HIV infection US\$16 per DALY (Gilson and others 1997) Kenya (E/D/STI) US\$11 to US\$16 per HIV infection US\$1 per DALY (Moses and others 1991)	South Africa (E/STI) US\$2,093 per HIV infection US\$105 per DALY (Wickerman and others forthcoming)	783	8
Antiretroviral therapy to reduce MTCT	No CE studies found	Mexico (M) US\$39,230 to US\$42,528 per HIV infection US\$2,124 to US\$2,303 per DALY (Rely and others 2003) India \$2,527 per HIV infection \$126 per DALY (World Bank 1999)	South Africa (M) US\$1,650 to US\$3,844 per HIV infection US\$66 to US\$154 per DALY (Wilkinson, Floyd, and Gilks 1998) Sub-Saharan Africa (M) US\$5,279 to US\$11,444 per HIV infection US\$211 to US\$458 per DALY (Marseille, Kahn, and Saba 1998) Sub-Saharan Africa (nevirapine) (M) US\$142 to US\$306 per HIV infection US\$6 to US\$12 per DALY (Marseille and others 1999)	320	3

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Table 18.4 Continued

Intervention	Epidemic profile (2001 US\$)			UNAIDS estimate of need for 2007		
	Low-level epidemic (Middle East and North Africa)	Concentrated epidemic (East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, South Asia)	Generalized low-level epidemic (Sub-Saharan Africa)	Generalized high-level epidemic (Sub-Saharan Africa)	2003 US\$ millions	Percentage of all prevention needs
MTCT, feeding substitution	No CE studies found	No CE studies found	No CE studies found	No CE studies found	—	—
Harm reduction for injecting drug users	No CE studies found	Belarus (E) US\$353 per HIV infection US\$18 per DALY (Kumaranyake and others 2004) Russia (E) US\$564 per HIV infection US\$28 per DALY (Bobrik 2004)	No CE studies found	No CE studies found	241	2
Drug substitution for injecting drug users	No CE studies found	No CE studies found	No CE studies found	No CE studies found	—	—
Blood safety	0.01–1 percent HIV prevalence (M/D/STIs) US\$374 to US\$45,173 per HIV infection US\$19 to US\$2,259 per DALY (Over and Piot 1996)	No CE studies found	Chad US\$75 to US\$151 per HIV infection US\$4 to US\$8 per DALY (Hutton, Wyss, and N'Diekhor 2003) Zambia (E/D/STI) US\$215 to US\$262 per HIV infection US\$11 to US\$13 per DALY (Watts, Goodman, and Kumaranyake 2000) Zambia (E) US\$41 per HIV infection US\$2 per DALY (Foster and Buve 1995)	Zimbabwe (E) US\$166 to US\$1,010 per HIV infection US\$8 to US\$51 per DALY (McFarland and others 1995)	230	2
						1–40 percent HIV prevalence US\$9 to US\$1,806 per HIV infection US\$0.45 to \$90 per DALY (Over and Piot 1996)

Sterile injection	Middle East (M) US\$393 per DALY (Dziekan and others 2003)	Southeast Asia US\$143 to US\$593 per DALY Americas US\$1,851 to US\$56,642 per DALY Western Pacific US\$953 per DALY (Dziekan and others 2003)	Africa US\$91 to US\$230 per DALY (Dziekan and others 2003)	94	1
Universal precautions	No CE studies found	No CE studies found	No CE studies found	663	7
Antiretroviral therapy for prevention and postexposure prophylaxis	No CE studies found	United States (E/S/no STIs) US\$76,584 per HIV infection US\$3,829 per DALY (Pinkerton, Holtgrave, and Bloom 1998)	No CE studies found	1	<1
Vaccines	No CE studies found	No CE studies found	No CE studies found	—	—
Behavior change for those who are HIV +	No CE studies found	No CE studies found	No CE studies found	112	1

Source: Authors.

— = not available.

CE = cost-effectiveness.

Note: The authors have categorized each of the studies. The first time each study is mentioned, it is identified by whether it was modeled (M) or empirical (E); whether it calculated primary HIV infections averted (S, for static) or if it also showed secondary infections averted (D, for dynamic); and where appropriate, we indicate if the study also looked at the impact on STIs. The cost-effectiveness of these interventions will differ depending on the population to which they are targeted, (that is, mass interventions versus targeted interventions). In addition, the cost-effectiveness of each intervention may vary greatly by study, because each cost-effectiveness study is not uniform. No cost-effectiveness studies of male condom promotion were found, because condom promotion, distribution, and IEC are generally part of a larger program with many components and studies did not distinguish between the costs of individual components of such programs.

## Box 18.2

### Comprehensive Sex Education Versus Abstinence-Only Education

The available data on sex education suggest the following:

- Sex education, including condom promotion, does not encourage or increase sexual activity (Kirby 2001).
- Sex education reduces risk and positively affects sexual behaviors. In general, sex education programs increase knowledge about AIDS and related issues, increase intention to use condoms, and increase condom use among sexually active youths (Kim and others 1997).
- Abstinence-only education is not effective in promoting healthy sexual behaviors. Programs that promote both postponement of intercourse and contraceptive use were more effective in changing behaviors than those that stressed abstinence alone. None of the abstinence-only programs that have been evaluated demonstrated an overall positive effect on sexual behavior, nor did they affect contraceptive use among sexually active participants (Kirby 1997).

Source: Authors.

methodological issues that will not be repeated here. The reviews agree that the availability of cost and cost-effectiveness analyses for HIV/AIDS prevention strategies is limited and that the need for such knowledge for planning and decision-making purposes is urgent.

Table 18.4 summarizes available cost-effectiveness estimates for the four UNAIDS epidemic profiles that are described later in table 18.5. The estimates of cost per disability-adjusted life year (DALY) saved assume a uniform 20 DALYs lost per infected adult (Murray and Lopez 1996) and 25 DALYs lost per infected child (Marseille and others 1999) and do not account for the increasing proportion of people living with HIV/AIDS in developing countries who will have access to antiretroviral therapy over the coming years.

#### **General Interventions Relevant for All Modes of Transmission**

The following are general interventions not specifically targeting the mode of transmission:

- *Information, education, and communication.* This intervention includes education on HIV/AIDS and condom use through pamphlets, brochures, and other promotional materials in classroom or clinic settings or through the radio, television, or press. In general, discerning the effectiveness of IEC alone is difficult, because IEC is often included in condom promotion and distribution interventions. Here we consider the effectiveness of IEC in concert with condom promotion and distribution. Of all available prevention interventions, providing information and education about HIV/AIDS is perhaps the most difficult to assess for cost-effectiveness. Numerous studies have shown that information alone is typically insufficient to change risk behavior. Accurate information, however, is indisputably the basis for informed policy discourse—a vital ingredient in the fight against fear-based stigma and discrimination. In
- the absence of studies to guide the level of investment in IEC, the only reasonable alternative seems to be to implement IEC on the basis of data derived from relative levels of knowledge and understanding in the population. For example, if only 25 percent of the sexually active population were able to describe how HIV is transmitted and prevented, clearly more IEC would be needed, but if 75 percent of the population understood the basic facts about HIV/AIDS, the need for additional funding would be diminished.
- *School-based sex education.* School-based sex education programs, an aspect of IEC, provide information to young people and reinforce healthy norms in a school setting (Peersman and Levy 1998). Limited data have shown differences in students who have been exposed to school-based sex education (summarized in table 18.3). Box 18.2 reviews the effectiveness of abstinence-only education and comprehensive sex education, subsets of school-based sex education. In light of more recent controlled studies that have not shown an effect on condom use, STIs, or HIV infection, any cost-effectiveness estimate is extremely speculative.
- *Voluntary counseling and testing.* This intervention enables people to know their HIV status and provides counseling support to help them cope with the outcome. Knowledge of serostatus may lead individuals to avoid engaging in risky behaviors (Sweat and others 2000). Cost-effectiveness estimates of VCT vary widely, and as with many other prevention interventions, these estimates are extremely sensitive to the prevalence of HIV in the population that is seeking testing.
- *Peer-based programs.* Peer interventions use influential members of a targeted community to disseminate information or teach specific skills. Such interventions have generally been found to be effective in reducing unsafe behaviors. Work on the cost-effectiveness of peer-based interventions in developing countries has been minimal. In Chad, Hutton, Wyss, and N'Diekhon (2003) reviewed data on 12 prevention

interventions and integrated them into a comparative analysis. Their findings suggest that peer education for sex workers is likely to be highly cost-effective and to entail one-fifth the cost of the next most favorable intervention, blood safety. However, the estimated cost-effectiveness for the same intervention directed toward young people and high-risk men is 33- to 36-fold lower.

**Interventions to Prevent Sexual Transmission** Below we discuss the effectiveness and cost-effectiveness of interventions that target sexual transmission of HIV:

- *Condom promotion, distribution, and social marketing.* Condom promotion, distribution, and social marketing vary by epidemic profile. The evidence on condom promotion and distribution programs indicates that such programs result in significantly higher condom use and significantly lower STI incidence (see table 18.3). Given the central role that condom promotion, distribution, and social marketing has played in HIV prevention programs, the lack of data on the relative cost-effectiveness of such programs 20 years into their implementation is striking. It is beyond dispute that the use of a condom by sexual partners who are HIV-discordant is extraordinarily cost-effective, given the low cost and high effectiveness of the condom in preventing HIV transmission. Information on the relative costs and effectiveness of different approaches to increasing condom use by serodiscordant sexual partners is not available, with the shortage of information being far more acute for effectiveness than for costs. In the absence of empirical evidence, decision makers are reduced to formulating policy on the basis of theory and common sense. Even inefficient use of condoms by seroconcordant couples is likely to be highly cost-effective because of the reduction in other STIs, cervical cancer, and unwanted pregnancies. However, more reliable information on

strategies to optimize the effectiveness and cost-effectiveness of condom programs is urgently needed.

- *STI screening and treatment.* The latest analyses suggest that STI control may be most effective as an HIV prevention strategy when initiated earlier in the course of national epidemics and when sexual risk behaviors are high (Orroth and others 2003). In most developing countries, the greatest benefits from treating STIs almost certainly accrue from averting the morbidity and mortality caused directly by STIs rather than indirectly because of reduced HIV transmission. Estimates of the cost-effectiveness of STI treatment purely as a way to reduce HIV transmission vary widely.

**Prevention of Mother-to-Child Transmission** The existing data on the effectiveness and cost-effectiveness of HIV interventions target MTCT in order of decreasing cost-effectiveness as follows:

- *Avoidance of unwanted pregnancies among infected mothers.* One of the most effective strategies to reduce HIV among infants is to provide better contraception services. See box 18.3 for details.
- *Use of antiretroviral therapy.* Evidence indicates that the provision of antiretroviral drugs to infected mothers significantly reduces vertical transmission (see table 18.4). The provision of antiretroviral therapy to prevent MTCT is highly cost-effective, to the point of being cost-saving for women who already know that they are infected. When screening of women is involved, cost-effectiveness declines as HIV prevalence falls, because of the larger number of women who must be screened to identify an HIV-positive woman (Rely and others 2003).
- *Feeding substitution.* Whereas in high-income countries the health community recommends complete avoidance of breastfeeding for HIV-infected mothers to prevent postnatal

### Box 18.3

#### Preventing Mother-to-Child Transmission: Antiretroviral Therapy or Contraception?

The differential effect of contraceptive delivery versus antiretroviral therapy in preventing HIV can be shown by comparing the provision of effective contraception and of nevirapine to a population of 1,000 HIV-infected women. In the absence of an intervention, approximately 150 infants would be infected with HIV during delivery (Cates 2004). If nevirapine were available, the number of infected infants would be reduced to 82 (the expected 47 percent decline). If effective contraceptive services were

available, this number would be reduced to 49. If both strategies were adopted, the number of infected infants would be further reduced to 25.

The greatest difference between providing antiretroviral therapy and providing contraception is the number of infants orphaned in the future because their mothers die of HIV infection. Three models all come to this conclusion (Reynolds and others 2004; Stover and others forthcoming; Sweat and others 2004).

Source: Authors.

HIV transmission, in developing countries the feasibility of this approach is often limited by such factors as cost, sustainability, lack of safe water, health, and child spacing and by sociocultural factors (Coutsoudis 2002). Prolonged breastfeeding more than doubles the likelihood of MTCT (Nduati and others 2000). Because evidence indicates that mixed feeding (breast milk and formula or other substance) has a higher risk of transmission than exclusive breastfeeding (Coutsoudis and others 1999), mothers should be counseled on the superiority of early weaning over mixed feeding. Even fewer data are available on the cost-effectiveness of feeding substitution.

**Prevention of Bloodborne Transmission** Below we discuss the effectiveness and cost-effectiveness of harm reduction for injecting drug users, implementation of blood safety practices, and provision of sterile injections:

- *Harm reduction for injecting drug users.* Harm reduction involves a combination of health promotion strategies for users, including needle and syringe exchange programs, ready access to effective drug treatment and substitution, and provision of counseling and condoms. Brazil, which has reduced the incidence of HIV and kept HIV prevalence from reaching projected levels, has relied on strong official support for harm reduction as a cornerstone of its national prevention program (Mesquita and others 2003). A limited number of studies have shown significant reductions in HIV incidence among those exposed to needle exchange programs, and several studies have shown significant reductions in needle sharing (see table 18.3). Methadone maintenance is both safe and effective as a treatment for drug addiction (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction 1998) and may help reduce the risk of HIV transmission by enabling individuals to avoid the drug-using behaviors that can lead to HIV infection (Metzger, Navaline, and Woody 1998; Needle and others 1998). However, the effect of drug treatment modalities on the rate of HIV transmission is currently limited by laws in many countries that prohibit or restrict the use of methadone maintenance or other drug substitution strategies. The evidence supporting the cost-effectiveness of needle exchange programs in high-income countries is strong. However, little has been published in relation to developing countries, partly because these programs have not been as widely implemented as hoped. Given the low cost of syringes, the extremely high efficiency of HIV transmission by this route, and the demonstrated effectiveness of harm reduction programs in changing syringe-sharing behavior, needle exchange programs should be one of the most cost-effective interventions.
- *Implementation of blood safety practices.* Transmission of HIV can be virtually eliminated in health care settings

through a blood safety program that ensures (a) a national blood transfusion service; (b) the recruitment of voluntary, low-risk donors; (c) the screening of all donated blood for HIV; and (d) the reduction of unnecessary and inappropriate transfusions (UNAIDS 1997). Available evidence indicates that HIV screening is effective in reducing HIV infections (see table 18.4). Blood screening for HIV is costly but has been shown to be cost-effective in numerous studies in developing countries (see table 18.3) (Foster and Buve 1995; Hutton, Wyss, and N'Diekhhor 2003; Watts, Goodman, and Kumaranayake 2000). The evidence appears to support the WHO and UNAIDS recommendations that all countries, regardless of the nature of the epidemic in the country, should implement a comprehensive blood safety program.

- *Universal precautions.* A critical component of standard infection control in health care settings is a prohibition on reusing needles and syringes. A controversy has recently arisen among researchers who contend that HIV infections have been significantly misclassified because of the undercounting of cases that result from unsafe injection practices by misattributing such cases to heterosexual transmission (Gisselquist and others 2003). However, after much investigation, WHO and the U.S. Department of Health and Human Services concluded that even though transmission caused by unsafe injections may have been underreported, it nevertheless does not account for an appreciable amount of HIV transmission (WHO and UNAIDS 2003). Cost-effectiveness analyses indicate that a combined policy strategy of single-use syringes and interventions to minimize injection use could reduce injection-related infections by as much as 96.5 percent, or 8.86 million DALYs between 2000 and 2030, at an average cost of US\$102 per DALY. Additional cost-effectiveness studies are needed to guide decisions regarding the optimal choice of technology in this area.

To prevent bloodborne transmission of HIV and other diseases, health care workers, emergency personnel, and others who might experience occupational exposure to blood or body fluids are advised to take universal precautions. This approach, which treats all bodily fluids as potentially infectious, includes the use of gloves, gowns, and goggles; the proper disposal of waste; and the use of sterile injection and other infection control practices (CDC 1989). Studies have demonstrated that the use of protective gear, such as gloves, reduces the likelihood of blood exposure in health care settings.

Although the cost-effectiveness of implementing universal precautions increases as HIV prevalence increases, universal precautions are unlikely to be cost-effective in resource-limited settings especially where HIV prevalence is low. Postexposure prophylaxis with antiretroviral agents is considered the standard of care after occupational needle-stick exposure to blood from an HIV-infected person.

Cost-effectiveness analyses of postexposure prophylaxis have been conducted only in high-income countries and have concluded that this intervention is not cost-effective (Low-Beer and others 2000; Pinkerton, Holtgrave, and Bloom 1998).

## PREVENTION IN THEORY AND PRACTICE: USING EPIDEMIC PROFILES AND CONTEXTUAL FACTORS TO INFORM PREVENTION GUIDELINES

Prevention studies and national experiences over the past 20 years strongly suggest that prevention strategies are likely to be most effective when they are carefully tailored to the nature and stage of the epidemic in a specific country or community. UNAIDS has developed epidemiological categories for characterizing individual epidemics on the basis of prevalence of infection in particular subpopulations and in the general population (table 18.5).

As a complement to the guidance provided by the epidemic profile, Grassly and others (2001) recommend assessing the prevalence of other STIs; estimating the extent of mixing between high- and low-risk groups (for example, men who have sex with men who have sexual contact with female partners); and estimating the prevalence of high-risk sexual behaviors in the population (such as lack of condom use with casual partners). They also cite two other critical contextual factors: the capacity of the health service and the social, economic, and legislative context, including social norms and attitudes about sexual and drug use behaviors and the acceptance of breastfeeding. Contextual factors that may play a role in the success of interventions include the status of women, the stigmatization of high-risk groups, and the presence of armed conflict and social upheaval. Together, the epidemic profile and the context in which the epidemic occurs suggest various prevention strategies.

### General Prevention Guidelines by Type of Epidemic

Generally, it is more important to change the behavior of people who have high levels of risk behavior than it is to change that of

people with lower levels of risk behavior. However, the difference in the effectiveness between the two falls as epidemics become more generalized, and as the average and maximum size of the connected components (number of people linked to each other directly or through others by their sexual or injecting risk behavior). Thus, in heavily affected countries, or those where the virus has the potential to spread rapidly, prevention interventions are likely to become extremely cost-effective even when targeted at individuals with relatively low levels of risk behavior. Consequently, countries with low-level and concentrated epidemics should emphasize interventions that target individuals at especially high risk of becoming infected or of transmitting the virus, whereas countries with generalized epidemics should also invest heavily in interventions that target entire populations or population subgroups. Thus, any determination of the likely effectiveness and cost-effectiveness of specific interventions in particular circumstances requires an accurate understanding of the stage and nature of the national epidemic.

The countrywide successes discussed in boxes 18.4 and 18.5 highlight population-level interventions that modify social norms as well as highlighting legislative and economic factors. Other examples include instituting government regulation of brothels and interventions to change social norms among sex workers in Thailand, implementing national sex education and blood safety programs in Senegal in concert with creating a national registry of sex workers, and mandating involvement by women in politics in Uganda.

**Low-Level Epidemic.** Providing widespread VCT, screening for STIs, universal precautions, and postexposure prophylaxis may not be cost-effective in a low-level epidemic. In this setting, such as in the Middle East and North Africa, HIV/AIDS control strategies should emphasize the following:

- surveillance and individual-level interventions that target key populations
- IEC, including limited education through the mass media and sex education in schools

**Table 18.5** Epidemic Profiles

Extent of HIV infection	Highest prevalence in a key population <sup>a</sup> (percent)	Prevalence in the general population (percent)	WHO region
Low level	< 5	< 1	Middle East and North Africa
Concentrated <sup>b</sup>	> 5	< 1	East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, South Asia
Generalized low level	≥ 5	1–10	Sub-Saharan Africa
Generalized high level	≥ 5	≥ 10	Sub-Saharan Africa

Source: Adapted from UNAIDS 2004.

a. Key populations include sex workers, men who have sex with men, and drug injecting users.

b. We consider three types of concentrated epidemics depending on the key population most affected: sex workers, men who have sex with men, or drug injecting users.

## Box 18.4

### Thailand's 100 Percent Condom Program

Thailand's HIV prevalence, fueled primarily by high rates of commercial sex work and low levels of condom use, began to rise rapidly in the late 1980s. Beginning in 1989, the Thai government initiated a nationwide condom distribution and education campaign focusing on commercial sex workers and their clients to ensure 100 percent condom use in all commercial sex encounters. Elements thought to contribute to the program's success include

- government-mandated 100 percent condom use in commercial sex establishments
- mass condom promotion advertising campaign
- education in commercial sex workplaces

Source: Authors.

- government-distributed condoms
- STI testing and treatment
- surveillance and tracking of infections to points of origin
- strong political and financial commitment
- active involvement of provincial and local governments.

Despite this unprecedented success, evidence indicates that enforcement of the 100 Percent Condom Program is not as strong today as when it was initially implemented. A recent study in Bangkok found that 89 percent of sex workers used condoms, a decline from 96 percent in 2000 (UNDP 2004).

## Box 18.5

### Uganda HIV/AIDS Prevention Program

Like many countries in Sub-Saharan Africa, Uganda experienced a rapid increase in HIV incidence and a generalization of the epidemic in the late 1980s and early 1990s. By 1991, overall HIV prevalence was 21 percent (Low-Beer and Stoneburner 2003); however, the trajectory of Uganda's epidemic has differed markedly from that of its neighbors. By 2001, overall HIV prevalence had fallen to 5 percent, with dramatic decreases in incidence among key populations, such as soldiers, pregnant women, and young women (USAID 2002). Critical components of Uganda's HIV prevention program include

- having strong political support, especially from President Yoweri Museveni

Source: Authors.

- implementing interventions to empower women and girls
- having a strong focus on youths
- engaging in active efforts to fight stigma and discrimination
- emphasizing open communication about HIV/AIDS
- engaging the religious leadership and faith-based organizations
- creating Africa's first confidential VCT interventions
- emphasizing STI control and prevention.

- prevention programs for people living with HIV/AIDS and harm reduction for injecting drug users
- VCT that is available to key populations with the highest levels of risk behavior and infection rates
- MTCT prevention to mothers known to be infected with HIV
- screening all blood for transfusions and providing sterile injections
- addressing market inefficiencies in condom procurement and distribution—including strategies such as bulk purchases and incentives

- responding to community attitudes toward sexual activity, as they may dictate people's response to sex education materials.

**Concentrated Epidemic.** In a concentrated epidemic, as in countries in East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, and South Asia, prevention priorities should include the following:

- ongoing surveillance
- subsidized VCT and promotion of VCT among key populations

- HIV screening of pregnant women, guided by individuals' risk profiles
- peer-based programs for key populations to educate individuals at risk, promote safer behaviors, and distribute condoms
- harm reduction for injecting drug users, including needle exchange and drug substitution programs
- STI screening and treatment for key risk groups
- targeted distribution and promotion of condoms to key populations with condom distribution linked to VCT and STI care.

In addition, contextual factors, such as government acceptance of needle exchange programs, incarceration of drug users, and harassment of sex workers, will likely have a major impact on the effectiveness of prevention efforts. Because HIV/AIDS is typically concentrated in socially or economically marginalized populations in countries with concentrated epidemics, attention to socioeconomic factors and to the stigmatization of key populations will also be vital to an effective response.

**Generalized Low-Level Epidemic.** In a generalized low-level epidemic, such as in some countries in Sub-Saharan Africa (for example, Tanzania), the emphasis on targeted interventions must be maintained or even strengthened. Interventions for broader populations must also be aggressively implemented. These prevention priorities should include the following:

- maintaining surveillance of STIs, risk behaviors, and HIV infections in the entire population, with a particular focus on young people
- extending mass media IEC beyond basic education
- providing routine voluntary and confidential HIV testing and STI screening and promoting treatment beyond key populations
- providing subsidized and social marketing of condoms and strengthened distribution to ensure universal access
- offering HIV screening to all pregnant women
- broadening peer approaches and targeted IEC to include all populations with higher rates of STIs and risk behavior.

Contextual factors remain critical to the success of prevention efforts in generalized low-level epidemics, but population-level factors now have greater priority. The most important is likely to be the status of women, especially with regard to their ability to control their sexual interactions, to negotiate VCT, to be protected from abuse, and to have property rights following the death of a spouse.

**Generalized High-Level Epidemic.** In a generalized high-level epidemic, such as in some countries in Sub-Saharan Africa (for instance, Botswana and Zimbabwe), an attack on all fronts is required. Prevention efforts should focus on broadly based,

population-level interventions that can mobilize an entire society so as to address prevention and care at all levels. Prevention should include the following:

- mapping and maintaining surveillance of risk behaviors, STIs, and HIV infection
- offering routine, universal HIV testing and STI screening and universal promotion of treatment
- promoting condom use and distributing condoms free in all possible venues
- providing VCT for couples seeking to have children
- counseling pregnant women and new mothers to make informed and appropriate choices for breastfeeding.
- implementing individual-level approaches to innovative mass strategies with accompanying evaluations of effectiveness
- using the mass media as a tool for mobilizing society and changing social norms
- using other venues to reach large numbers of people efficiently for a range of interventions—workplaces, transit venues, political rallies, schools and universities, and military camps
- establishing official institutional policies to provide for harm reduction among injecting drug users.

In a generalized high-level epidemic, contextual factors—such as poverty and the fragility of the health care infrastructure—will dramatically affect service provision at every level. The status of women, an important factor in all epidemics, becomes an overriding concern in this setting, requiring priority action to radically alter gender norms and reduce the economic, social, legal, and physical vulnerability of girls and women.

## PREVENTION-CARE SYNERGY

In addition to the benefits antiretroviral therapy has for the individual being treated (Komanduri and others 1998; Ledergerber and others 2001), it almost certainly has other effects on populations where therapy is widely available. Effective antiretroviral therapy appears to decrease the infectiousness of treated individuals. Chemoprophylaxis in exposed, uninfected people may reduce transmission. In addition, availability of treatment may destigmatize the disease and make prevention programs more effective (Castro and Farmer 2005).

However, these benefits in relation to reduced transmission may be offset by a “disinhibition” of risk behavior that is associated with greater availability of antiretroviral therapy, by the spread of drug-resistant HIV, or by increases in the incidence of exposure to partners with HIV infection because of increased survival. These sometimes opposing effects of offering therapy may differ to such a degree that the net effects of widespread therapy on transmission rates may vary among risk groups and across geographic regions.

**Table 18.6** Effect of Antiretroviral Therapy on Transmission Dynamics

Area or behavior affected	Treatment effects expected to decrease transmission	Treatment effects expected to increase transmission
Viral load	Decreased infectiousness of the treated partner is substantial even with monotherapy (Musicco and others 1994). Transmission after exposure to individuals with a viral load of less than 1,500 copies per milliliter is extremely rare (Quinn and others 2000). No cases of sexual transmission from a partner with undetectable viremia have been reported.	As survival increases, the incidence of exposure to partners with HIV infection may increase (Hammer and others 1997).
Prophylaxis	Decreased susceptibility may occur during postexposure prophylaxis (Cardo and others 1997).	None.
Drug resistance	Impaired fitness and decreased viral load during drug-resistant viremia (Deeks and others 2000) appear to allow persistent decreases in infectiousness even after drug resistance has occurred (Leigh Brown and others 2003).	Impaired virological responses to therapy in the person who is infected by a resistant virus may partially offset the beneficial effect on infectiousness (Little and others 2002; Grant, Kahn, and others 2002). However, primary infection with a resistant virus may also be associated with slower progression of the disease (Grant, Hecht, and others 2002).
Risk behavior	Treatment may provide incentives for HIV testing and counseling, which has been associated with decreased risk behavior and HIV incidence. The availability of treatment may reduce stigma directly, and also indirectly by increasing the visibility of people living with HIV/AIDS.  Risk reduction counseling during treatment programs may reduce risk behavior.	Decreased fear of HIV and disinhibition of risk behavior are possibilities (Katz and others 2002). Risk behavior by people who are sick and who recover their health status may increase (Stolte and others 2001).
Sexual networks	Decreased fear of HIV may foster more informed risk behavior, including increased use of testing and more thoughtful partner selection, including serosorting and sorting by risk level (McConnell and Grant 2003).	Decreased fear of HIV may disinhibit risk behavior, reduce serosorting, and increase mixing between higher- and lower-risk groups in the population.
Epidemiological	The effective prevalence of infectious people will decrease because of treatment effects on infectiousness or increased serosorting.	Treatment-induced reduction in mortality may increase the prevalence of infection, although many being treated will be less infectious or better informed regarding risk reduction strategies. A rebound of viral load with treatment failure may mean that treatment postpones transmission rather than reducing it.

Source: Authors.

Table 18.6 reviews the information available on the population effects of antiretroviral therapy and makes suppositions about potential effects for those areas for which data and research are lacking. The information in the table suggests that widespread therapy using currently available combination regimens will provide a net benefit in relation to the transmission of HIV. However, because confidence in this prediction is not high, the population consequences of therapy programs must be evaluated and monitored with active surveillance of prescribing patterns, sexual risk behavior, STI prevalence, HIV incidence and prevalence, and prevalence of primary drug resistance and sexual networks of risk behavior.

## CARE AND TREATMENT

This section reviews evidence of the cost-effectiveness of HIV/AIDS care and treatment interventions in resource-limited settings. Until relatively recently, the majority of HIV

clinical care in resource-limited countries was confined to managing the terminal stage of infection, including extremely late diagnosis of opportunistic infections and cancers, use of basic palliative symptom management, and short-term hospitalization just before death. Few people were aware of their HIV status until the onset of severe HIV-associated illness, and most did not seek help from the health care system until they were already terminally ill.

The advent of primary prophylaxis and treatment for opportunistic infections, including tuberculosis, prolonged survival to a limited extent but did nothing to restore immune function. Such restoration was not possible until the advent of antiretroviral therapy. Because clinical intervention in HIV is so recent in resource-limited settings, few cost-effectiveness studies are available. Those that are available on the treatment of and prophylaxis for opportunistic infections were largely conducted before the availability of antiretroviral therapy and therefore need to be reestimated to be relevant for decision

making today. Fortunately, because the determinants of biological responses are better conserved across countries and cultural settings than the determinants of behavior, effectiveness data from high-income countries can help inform decisions about treatment in resource-limited settings.

Unlike drugs for many other high-burden health conditions in developing countries, antiretroviral therapy for HIV and drugs for some of its associated opportunistic infections depend on medications that are still under patent protection. Nevertheless, generic drug makers in India and Thailand have produced a range of effective antiretroviral therapies that combine multiple drugs into single tablets and reduce the pill burden to one tablet twice daily. These companies have made it possible for prices to drop dramatically for some antiretroviral therapy combinations—to less than US\$250 per year, compared with more than US\$4,000 for the same combinations (from the original manufacturers) in high-income countries. In response to this threat, some multinational pharmaceutical companies have introduced a system of price differentiation among countries depending on their per capita income and HIV/AIDS burden.

In addition, the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) includes a provision that permits compulsory licensing of pharmaceutical products in cases of national emergency and other circumstances of extreme emergency, which is clearly the case for HIV/AIDS in much of the developing world. A 2003 World Trade Organization decision also made it easier for low- and middle-income countries (LMICs) to import cheaper generics made under compulsory licensing if the countries are unable to manufacture the medicines themselves (WTO 2003). As a result, some countries, including Brazil, India, and Thailand, have begun to produce generic versions of antiretroviral drugs to be sold at greatly reduced prices. The TRIPS provision has also improved developing countries' bargaining power with large pharmaceutical companies, to the point that some countries have been able to secure drugs from the original manufacturers at substantially reduced prices. As a result, the relative cost-effectiveness of different drug combinations has been in rapid flux, increasing the importance of updating recommendations frequently.

### Diagnostic HIV Testing

A positive HIV test can be confirmed within one month of infection. Infection is diagnosed in two ways: by a biological test that detects the presence of HIV antibodies or by diagnosis of an opportunistic infection that is a clear sign of HIV disease. The most widely used biological test in high-income countries, conducted in a laboratory on a blood sample, is called an ELISA (enzyme-linked immunosorbent assay). Obtaining a result may take several days. Rapid tests that can provide results in 20 minutes are being used more widely as their costs fall. When the prior probability of infection is low and resources are

abundant, following up an initially positive ELISA with a second ELISA—and even a Western blot test if the second ELISA is positive—may be appropriate (this is typically done in high-income countries).

However, in a high-prevalence environment where the prior probability is high and resources are scarce, such an approach is almost certainly not cost-effective. Each additional confirmatory test decreases the number of false positive results, thereby averting the costs associated with such a result. The costs of averting a false positive result range from US\$425 with a single confirmatory rapid test or ELISA to more than US\$500,000 for a confirmatory Western blot test following two positive ELISAs as the prevalence of HIV in patients who are clinically suspected of being infected is varied from 5 to 50 percent (these calculations are based on assumptions in John Snow, Inc. 2003 and WHO 2004). These results suggest that LMICs should not use a second confirmatory test unless the prevalence among patients is extremely low.

### Palliative Care

Palliative care has traditionally focused on patients in the terminal stages of disease. More recent definitions of palliative care, including WHO's definition, have been broadened to encompass quality-of-life issues of patients and their families throughout the course of a life-threatening illness (WHO 2002b). The control of pain and other symptoms is the crux of any palliative care model, but the WHO model also addresses patients' and their families' psychological, social, and spiritual problems. Under this definition, in many developing countries, most people living with HIV/AIDS are not receiving the minimum standard of palliative care. Of the 5 million people living with HIV/AIDS in South Africa, one of the wealthiest countries in Sub-Saharan Africa, Carlisle (2003) estimates that only 250,000 have access to palliative care services. In the face of a growing epidemic of historic dimensions, the provision of comprehensive palliative care represents a critical, but neglected, global priority.

Health care professionals have promoted community home-based care as an affordable way to expand the coverage of palliative care (Hansen and others 1998), but the great heterogeneity among home-based care programs complicates comparisons. Most programs for which data are available are community-based outreach programs administered by local clinics or hospitals. These programs can consist of simple home visits to provide basic care for AIDS patients or may be comprehensive schemes that provide care, palliative medications, meals, psychosocial support and counseling, and links to primary and secondary health care.

Studies indicate that home-based care has considerable potential to deal cost-effectively with the palliative care needs of HIV/AIDS patients (Ramsay 2003; UNAIDS 2001; Uys and Hensher 2002; Wenk, Bertolino, and Pussetto 2000). Although

a Zimbabwe study found that home visits were associated with extensive travel time and costs (Hansen and others 1998), little research has examined the extent to which home-based care can be used to substitute for hospitalization, nor is evidence available to determine the most cost-effective combination of palliative care strategies. Most people living with HIV/AIDS do incur some end-of-life costs in the formal health care sector. In one South African study, primary care clinic and hospital costs accounted for 39 and 18 percent, respectively, of the costs of care in the last year of life, whereas community home-based care accounted for 42 percent (Uys and Hensher 2002).

Higginson and others' (2003) meta-analysis concludes that overall evidence demonstrates a positive effect of home-based palliative care, especially its effect on pain management and symptom control. Available data do not permit estimating a cost per DALY of community-based palliative care programs, but a review of available studies suggests that palliative care provided by health professionals in the home is unlikely to be cost-effective in low-income countries. However, low-cost, community-based models have been developed that require minimal external resources and function almost like care cooperatives among affected households. These models are likely to be highly cost-effective.

**Symptom-Based Care.** Pain management is extremely important in HIV and is addressed in chapter 52. Diarrhea, nausea, vomiting, and skin problems are all symptoms that are targeted for treatment in palliative care. Oral rehydration for diarrheal treatment costs pennies per episode. Nausea and vomiting are prevalent in people with AIDS and can lead to anorexia and weight loss (UNAIDS 2000). Treating nausea costs an estimated US\$1.75 per episode (Willbond and others 2001), and continuous treatment of nausea and vomiting in end-stage patients costs about US\$2 per day (World Bank 1997).

Approximately 90 percent of people with HIV suffer from some form of skin condition. These conditions include infections, drug reactions, scabies, pressure sores, and cancers. Skin often becomes dry in the middle and late stages of AIDS because of dehydration caused by persistent diarrhea, vomiting, and malabsorption. The cost of treating an episode of skin rash is estimated to be US\$2 (UNAIDS 2000). No estimates are available on the benefits of providing such care in terms of DALYs, especially to terminally ill patients.

**Psychosocial Support.** Psychosocial support is an integral component of the multidisciplinary management strategies that care providers regard as essential for people with HIV (Murphy and others 2004). Support for patients and families can have a positive effect on adherence to therapies and can contribute to the critical aim of integrating prevention with treatment and care.

Psychosocial support and counseling has a positive effect on the quality of life of people living with HIV/AIDS. Cook's

(2004) study of U.S. women demonstrated that the use of mental health services was associated with reduced mortality and that AIDS-related deaths were more likely among women who had symptoms of chronic depression. While results have not been replicated in resource-constrained countries, an assessment of clinic-based psychosocial support and counseling services in northern Thailand showed that 50% of PLWHA became more positive about their lives and 40% stated that they learned how to live with the disease (Tsunekawa and others 2004). Although few data are available on the costs of various strategies, interventions for psychosocial support appear to be cost-effective—especially where innovative solutions, such as group counseling sessions, are implemented. Although studies indicate an improved quality of life for these patients, little information is available on the cost of the interventions. Additional evaluation research is needed to guide decisions about how much to invest in psychosocial support.

**Nutrition Programs and Food Security.** Strong evidence indicates that malnutrition and AIDS work in tandem at both the individual and the societal levels. Infection with HIV increases the risk of malnutrition in the individual, while malnutrition worsens the impact of HIV and AIDS. Similarly, HIV/AIDS can both cause and be worsened by food insecurity. This reciprocity must be considered when planning specific program responses.

Protein deficiency is a well-known cause of cell-mediated immunodeficiency (Vanek 1953). HIV-infected individuals need to consume more energy than uninfected individuals: as much as 10 percent greater consumption for asymptomatic individuals and 20 to 30 percent more for symptomatic individuals. Malnutrition alters the susceptibility of individuals to HIV infection and their vulnerability to its various sequelae, increases the risk of HIV transmission from mothers to babies, and accelerates the progression of HIV infection (Gillespie, Haddad, and Jackson 2001).

Small studies of adults with AIDS, including those on anti-retroviral therapy, have shown that daily micronutrient supplementation increases bodyweight, reduces HIV RNA levels, improves CD4 counts, and reduces the incidence of opportunistic infections. Fawzi and others' (2004) large trial among pregnant women infected with HIV in Tanzania demonstrates that multivitamin supplements (a) decrease the risk of progression to WHO stage 4 (progression from HIV to AIDS, the most advanced level of HIV infection) or death from AIDS-related causes and (b) reduce many HIV-related symptoms. The multivitamins used in the trial cost US\$15 per person per year (Fawzi and others 2004).

The World Food Program guidelines prioritize three nutrition interventions for people living with HIV/AIDS: counseling on specific behaviors, prescribed or targeted nutrition supplements, and links with food-based interventions and

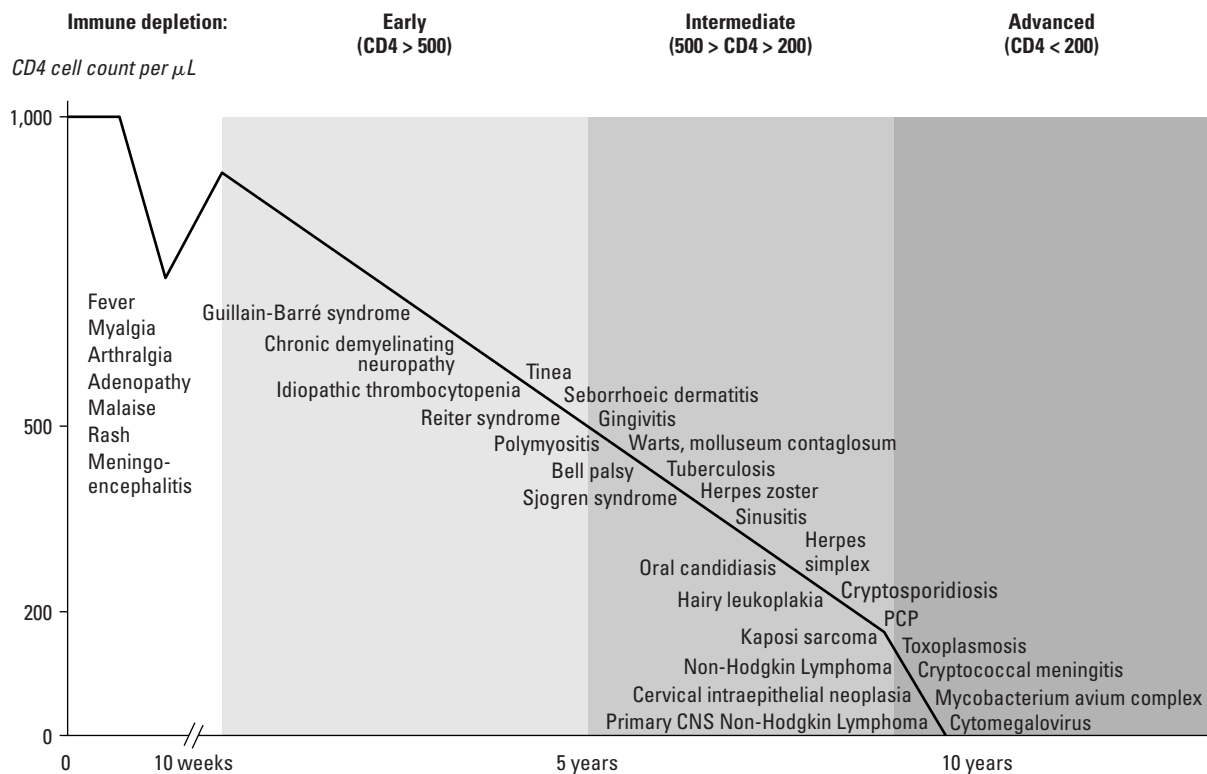
programs. The guidelines cite three types of nutrition supplements: food rations to manage mild weight loss and nutrition-related side effects of antiretroviral therapy and to address nutritional needs in food-secure areas; micronutrient supplements for specific HIV-positive risk groups; and therapeutic foods for addressing moderate and severe malnutrition in HIV-positive adults and children. Cost-effectiveness data in support of these recommendations are not available, but the low costs of supplementation, coupled with the likely benefits to other malnourished household members, suggest that such interventions will be highly cost-effective.

Infection with HIV/AIDS can severely undermine an individual's food security, affecting the availability, stability, access to, and use of essential foods. The epidemic is stunting progress in rural development and causing significant increases in rural poverty and destitution in the countries most affected by the epidemic (Bonnard 2002). Thus, interventions must consider the epidemic's impact on the broader community and not solely on people living with the disease. Care-related household and community-level interventions include school feeding with special take-home rations for families caring for orphans, food for training programs that promote income-generating activities, and food for work to support homestead production

activities (Van Liere 2002). Chapter 56 estimates that sustained community nutrition programs would *save* US\$200 to US\$250 per DALY. Such programs targeted at communities at especially high risk are likely to be even more cost-effective (World Food Programme 2001).

### Treatment of Opportunistic Infections and Secondary Prophylaxis

Even as the availability of antiretroviral therapy increases in many developing countries, appropriate diagnosis and management of life-threatening opportunistic infections, including HIV-associated cancers, remain the most important aspects of the care of patients with HIV disease. Opportunistic infections usually begin five to seven years after infection (Munoz, Sabin, and Phillips 1997) and occur progressively as uncontrolled HIV replication destroys the immune system (Colebunders and Latif 1991). Figure 18.1 describes the cascade of infections that occur as the immune system is depleted. Opportunistic infections are typically caused by organisms that exist in the environment of the body (on the skin, in the lungs and gastrointestinal system) and remain latent until HIV has impaired the immune system.



**Figure 18.1** Cascade of Infections and Cancers That Develop as Immune Function Is Depleted

The epidemiology of opportunistic infections is complex; it is related to the severity of individual immune depletion and shows considerable intercountry variation. Each infection has its unique clinical expression, requiring specific diagnostic techniques and treatment. Many opportunistic infections can be prevented by judicious use of chemoprophylaxis, ranging from the low-cost (cotrimoxazole to prevent *Pneumocystis jiroveci* pneumonia [PCP] at less than US\$20 per year) to the extremely expensive (ganciclovir to prevent cytomegalovirus at more than US\$10,000 per year) (Schneider and others 1995; Spector and others 1996). In high-income countries, antiretroviral therapy has so effectively controlled viral replication that the process of HIV-related immune destruction has been slowed or halted, leading to marked declines in the incidence of opportunistic infections and a dramatic reduction in their resultant high death toll (McNaghten and others 1999). Unfortunately, the emerging problem of poor adherence to drug regimes is now making HIV resistance to antiretroviral therapy more prevalent in high-income countries, triggering a resurgence of opportunistic infections.

More than 20 infections and cancers have been associated with severe immune depletion. The most common pathogens and cancers include bacteria such as *Mycobacteria tuberculosis* and *avium*; protozoa such as *Cryptosporidium*, *Strongyloides*, and *Toxoplasma*; fungi such as *Candida*, PCP, *Cryptococcus*, *Aspergillus*, and *Penicillium* (the latter largely restricted to South and Southeast Asia); viruses such as cytomegalovirus, herpes simplex, and herpes zoster; and cancers such as Kaposi sarcoma and non-Hodgkin lymphoma.

The range of complications arising from continued HIV infection varies from country to country, reflecting the differences in infectious agents that populations have encountered earlier in life or are exposed to when immunosuppressed. In high-income countries, the most common opportunistic infections are PCP, esophageal candidiasis, cytomegalovirus retinitis, cryptococcal meningitis, toxoplasma encephalopathy, cryptosporidium diarrhea, and human herpes virus-8 and Kaposi sarcoma (Bacellar and others 1994; Hoover and others 1993; Lanjewar and others 1996; Selik, Starcher, and Curran 1987). In resource-limited countries, because of the higher background prevalence of infectious agents, it is more common to encounter tuberculosis, cryptococcal meningitis, toxoplasma encephalopathy, infectious diarrhea, and nonspecific wasting (slim disease) (Hira and others 1998; Hira, Dore, and Sirisanthana 1998a; Sengupta, Lal, and Srinivas 1994).

The time from HIV infection to manifestation of the first AIDS-defining illness varies within populations. In high-income countries, reports on the natural history of untreated HIV infection suggest that AIDS occurs between 7 and 10 years after infection (Alcabes and others 1993; Lui and others 1988). The time can be as short as 24 months (Anzala and others

1995) in some individuals, whereas some long-term survivors remain disease free for longer than 15 years (Easterbrook 1994). In developing countries, disease progression, though not as well studied, appears to be more rapid (Morgan and others 1997). Once an AIDS-defining illness occurs, the average time to death seems to be similar across countries, reported at approximately 12 to 18 months in Uganda and the United States (Carre and others 1994).

The time from presentation with an AIDS-defining opportunistic infection to death depends on the type of infection, the availability of care, and the patient's adherence to prescribed prophylaxis and treatment. Even as access to antiretroviral therapy increases, prophylaxis for opportunistic infections remains one of the most important ongoing and successful care strategies for patients with advanced HIV disease. In high-income countries, the widespread use of such simple interventions as cotrimoxazole for PCP prophylaxis has had a significant effect in delaying the onset of PCP, the most common initial AIDS-defining event, thus positively influencing survival (Hoover and others 1993). However, prophylaxis for opportunistic infections appears to be underused in LMICs.

Prevention of PCP or any other opportunistic infection does not halt the relentless erosion of the immune system and provides only a short-term prolongation of life (Morgan and others 1997). The only way to halt or delay the progression of HIV disease is to interrupt viral replication.

**Role of Antiretroviral Therapy in Relation to Opportunistic Infections.** Antiretroviral therapy is effective in reducing viral load and partially enabling immune restoration, thereby preventing the onset and recurrence of opportunistic infections. If taken strictly according to directions, antiretroviral therapy can induce a sustained recovery of CD4 cell reactivity against opportunistic pathogens in severely immunosuppressed patients (Li and others 1998). The effectiveness of antiretroviral therapy is determined by its ability to rapidly reduce viral load and to sustain low levels of viral activity. This viral activity is what has an independent effect on increasing or decreasing susceptibility to opportunistic infections (Kaplan and others 2001).

Initiating antiretroviral therapy can also have detrimental effects by causing complications from latent or undiagnosed opportunistic infections, especially in resource-poor settings. One of the challenges in initiating antiretroviral therapy in resource-limited settings is that patients tend to present late in their illness, usually when they have an opportunistic infection that prompts them to seek medical care, or in the case of countries with lax pharmaceutical policy, when they buy antiretroviral therapy from a private pharmacy. It is well documented that initiating antiretroviral therapy in severely immunosuppressed patients can result in illnesses associated with reconstitution of the immune system (Shelburne and

others 2005). These illnesses can occur with all presenting opportunistic infections and may be more serious than the infection itself. The major problem with care of patients in this situation is that they may believe the illness is a side effect of their antiretroviral therapy and refrain from medicating. Training clinicians to recognize and treat immune reconstitution disease is therefore essential.

**Management of Opportunistic Infections.** The three components of effective management of opportunistic infections are diagnosis, treatment, and secondary prophylaxis. As immune function continues to deteriorate, secondary prophylaxis is required to prevent recurrence of the treated infection. Some of the most common infections, such as PCP, can be diagnosed with a reasonable degree of confidence by clinical history and treated empirically (Kaplan, Masur, and Holmes 2002). Less frequently occurring infections often require sophisticated diagnostic equipment and skilled clinicians to confirm a diagnosis from a wide range of pathogenic possibilities before starting complex and expensive treatment. For example, toxoplasmosis can be accurately diagnosed only by a lumbar puncture and CT brain scan (and in some cases an MRI), and cryptosporidium diagnosis requires specialized laboratory techniques.

The full spectrum of options for treating opportunistic infections in developing countries has not been systematically evaluated for cost-effectiveness. Because of the effect of antiretroviral therapy on both the efficacy of treatment of individual infections and on life expectancy (and therefore on potential DALYs gained from treating a life-threatening infection), the limited economic evaluations conducted are already out of date. In particular, chronic infections such as *Mycobacterium avium* complex and cytomegalovirus may be more effectively treated over the medium term by reversing immunosuppression with antiretroviral therapy than by directly treating the infectious agent. Other treatment regimens for opportunistic infections that were marginally cost-effective before antiretroviral therapy may now become substantially more cost-effective if the patient can begin the therapy following treatment of the infection, thereby extending life expectancy. Table 18.7 shows the cost-effectiveness of care and treatment options for opportunistic infections and antiretroviral therapy.

In most resource-limited settings, few specialized diagnostic facilities are available for opportunistic infections. Clinicians have little training in the diagnosis and management of complex opportunistic infections, and laboratory backup is either nonexistent or so expensive that end users cannot afford it. The spectrum of opportunistic infections in LMICs is such that most require highly technical facilities for confirmation of diagnosis. Consider *M. tuberculosis*, the most prevalent such infection in Thailand. The rate of latent tuberculosis becoming clinically active in the presence of HIV increases from a lifetime

risk of 10 percent in the general population to an annual risk of 10 percent for those coinfecting with HIV (Pape and others 1993). Hence, after five years, about 40 percent of HIV-infected people with latent tuberculosis will have developed active disease.

### **Primary Prophylaxis for Opportunistic Infections**

Before the advent of antiretroviral therapy, the use of prophylaxis to decrease the risk of acquiring opportunistic infections was the only intervention available to delay the onset of life-threatening infections (Kitahata and others 1996). With the development of antiretroviral therapy in the 1990s, the prevalence of many opportunistic infections has been greatly reduced, and the use of prophylaxis has decreased correspondingly (Palella and others 2003). Nevertheless, prophylaxis for opportunistic infections remains necessary in patients who lack access to antiretroviral therapy, in extremely immunosuppressed patients until the therapy takes effect, in patients who do not wish to or who cannot take antiretroviral therapy, in patients for whom such therapy fails, and in the small group of patients who are unable to recover sufficient CD4 cells despite good inhibition of viral replication (Berenguer and others 2004). Note that extensive clinical research is still being carried out in relation to the withdrawal of secondary prophylaxis following immune restoration with antiretroviral therapy.

### **Treatment of HIV Infection with Antiretroviral Therapy**

Combination therapy with multiple antiretroviral drugs is associated with prolonged survival. Whereas monotherapies are associated with one year or less of additional survival, the survival benefit conferred by combination therapy appears to be sustainable for extended periods (Palella and others 2003). Long-term toxicities related to treatment may include atherosclerosis, lipodystrophy, hepatic failure, and cardiac failure. Researchers are still evaluating the effects of these toxicities on HIV/AIDS mortality.

### **Cost-Effectiveness Considerations in the Choice and Initiation of Antiretroviral Therapy.**

WHO has issued global guidelines for scaling up antiretroviral therapy access; the guidelines promote a combination of stavudine, lamivudine, and nevirapine (as a fixed-dose formulation) as initial therapy. A number of clinical trials have produced results outlining differential efficacy for a number of antiretroviral therapy combinations, which provide guidance in the selection of appropriate drugs for treating HIV (Yeni and others 2004). The preferred first-line medications in developing countries are dictated by these considerations, in addition to pricing and patent concerns.

**Table 18.7** Cost-Effectiveness of Care and Treatment for HIV/AIDS

Intervention	Source	Cost-effectiveness (2001 US\$/DALY)	
		Before or when initiating antiretroviral therapy	Failed or no antiretroviral therapy
<i>HIV testing and diagnosis</i>			
Confirmatory ELISA, Western blot	No cost-effectiveness studies found in developing countries	—	—
<i>Palliative care</i>			
Pain alleviation	Chapter 52	420/year of pain-free life added	420/year of pain-free life added
Symptom-based care	No cost-effectiveness studies found in developing countries	—	—
Nutrition interventions	Chapter 56	200–250 for HIV-negative individuals	200–250 for HIV-negative individuals
End-of-life care	No cost-effectiveness studies found in developing countries	—	—
<i>Treatment of opportunistic infections, per episode</i>			
Oral candidiasis	Modeling estimates based on efficacy trials reported from HIVInsite (CHI, 2005) and drug costs (UNICEF and others 2004)	0.5–157	1–394
Esophageal candidiasis		0.4–55	1–165
Histoplasmosis		12–77	81–539
Kaposi's sarcoma		6,236–63,700	12,460–127,400
Cryptococcal meningitis		3–86	21–546
Penicilliosis		11–72	76–483
Mycobacterium avium complex		31–51	87–320
Cytomegalovirus		586–995	4,875–5,120
PCP		0.4–5	3–35
Toxoplasmosis		5–44	31–291
Herpes simplex virus		3–32	7–80
Tuberculosis	Chapter 16	200–370	50–450
	South Africa (Floyd, Wilkinson, and Gilks 1997); Malawi, Mozambique, Tanzania (Murray and others 1991); Uganda (Saunderson 1995)	Short-course ambulatory: 2–16 Short-course hospital: 3–8 Community-based directly observed therapy: 14–22	Short-course ambulatory: 2–16 Short-course hospital: 3–8 Community-based directly observed therapy: 14–22
<i>Opportunistic infection prophylaxis</i>			
PCP	Modeling estimates based on efficacy trials reported from HIVInsite (CHI, 2005) and drug costs: (UNICEF and others 2004)	29–1487	590–29,817
Toxoplasmosis		14–412	252–8,265
Mycobacterium avium complex		786–3,604	2,247–18,020
Cytomegalovirus		151,855–972,955	976,209–4.5 million
Tuberculosis preventive therapy	Uganda (Bell, Rose, and Sacks 1999); Chapter 16	15–300 (Isoniazid, Rifampicin plus pyrazinamide, Isoniazid plus rifampicin)	15–300 (Isoniazid, Rifampicin plus pyrazinamide, Isoniazid plus rifampicin)
<i>Early detection and screening for opportunistic infections</i>			
HPV screening and treatment	South Africa (Goldie and others 2001)	Direct visual inspection using acetic acid: < 4/years of life saved	Direct visual inspection using acetic acid: < 4/years of life saved
<i>Antiretroviral therapy</i>			
First-line antiretroviral therapy	Sub-Saharan Africa (Marseille, Hofmann, and Kahn 2002)	350	350
Second-line (and subsequent) antiretroviral therapy	India (Over and others 2004)	492/patient year <sup>a</sup>	492/patient year <sup>a</sup>
	No cost-effectiveness studies found in developing countries	—	—
Adherence interventions	No cost-effectiveness studies found in developing countries	—	—
Monitoring response to antiretroviral therapy	No cost-effectiveness studies found in developing countries	—	—

Source: Authors.

— = not available.

a. Antiretroviral therapy for the poorest HIV positive adults. The estimates include the cost of drugs, clinic visits, and laboratory tests for physician monitoring of treatment and assumes 50 percent condom use in the general population.

## Box 18.6

### Antiretroviral Drugs

Current antiretroviral drugs can be divided into three classes:

- *Nucleoside analogue reverse transcriptase inhibitors* (NRTIs) were the first type of drug available to treat HIV infection in 1987. When HIV infects a cell, it copies its own genetic code into the cell's DNA, and the cell is then programmed to create new copies of HIV. To reproduce, HIV must first convert its RNA into DNA using the enzyme reverse transcriptase. Nucleoside analogue reverse transcriptase inhibitors act like false building blocks and compete with the cell's nucleosides, thereby preventing DNA synthesis. This inhibits reverse transcriptase, which prevents HIV from infecting cells and duplicating itself.
- *Nonnucleoside reverse transcriptase inhibitors* (NNRTIs) started to be approved in 1997. Like nucleoside analogue reverse transcriptase inhibitors, nonnucleosides also interfere with HIV's ability to infect cells by targeting reverse transcriptase. In contrast to nucleoside analogue reverse transcriptase inhibitors, nonnucleosides bind directly to the enzyme. This blocks the binding site of the reverse transcriptase and inhibits the binding of nucleotides.
- *Protease inhibitors* (PIs) were first approved in 1995. PIs interfere with viral replication by binding to the viral protease enzyme and preventing it from processing viral proteins into their functional forms and thereby rendering the resulting viral particles non-infectious (Peiperl, Coffey, and Volberding 2005).

Source: Authors.

In recent years, the most volatile parameter in cost-effectiveness analyses for HIV/AIDS has been the prices of antiretroviral drugs, which have dropped by about two orders of magnitude for some LMICs. Price reductions have not been consistent across countries, nor have they necessarily been larger for the poorest countries. This variability in pricing greatly complicates the establishment of national guidelines regarding which regimens to prescribe under which circumstances, because the ranking of regimens varies among and within countries as relative prices change. Box 18.6 discusses the three classes of drugs used in antiretroviral therapy.

Because of their higher manufacturing costs and their more recent introduction into the market, protease inhibitors are more expensive than either nucleoside reverse transcriptase inhibitors or nonnucleoside reverse transcriptase inhibitors. They are also more difficult to manufacture, making them less attractive to generic manufacturers. Although the difference is less marked, nucleoside reverse transcriptase inhibitors tend to cost less than nonnucleoside reverse transcriptase inhibitors.

Ranking different antiretroviral therapy regimens by their cost-effectiveness is more complex than doing so for most therapeutic situations, because a high proportion of patients will develop resistance to or intolerance of initial therapy and will need to stop their initial regimen and then initiate a second (and perhaps a subsequent) regimen, if available. One U.S. cohort study suggests that for 50 percent of patients the

prescribed protease inhibitor-based regimen fails within a year (Deeks and others 1999). As a result, the cost-effectiveness of a regimen is a function not only of its effectiveness in isolation, but also of its impact on the effectiveness of future regimens. Thus, the comparative cost-effectiveness of different sequences of regimens needs to be considered.

The effectiveness of antiretrovirals depends on not only the benefits conferred but also the associated side effects, the toxicity level of the drugs, and patients' adherence to the drug regimen. The ability of care providers to detect incipient toxicity at an early stage also influences the magnitude of side effects and toxicities. In low-income settings with limited laboratory capacity, a greater proportion of side effects will not be detected until they become severe. As a result, the relative cost-effectiveness profiles will change depending on the availability of toxicity monitoring.

Initiating antiretroviral therapy has a proven benefit for patients with a CD4 count of fewer than 350 cells per cubic millimeter (Palella and others 2003). In patients with a higher CD4 count, the benefits of antiretroviral therapy are believed to be outweighed by the toxicities that may accrue from continued drug exposure (Mallal and others 2000). Concerted research efforts are needed to gauge both the average costs of care and the survival benefits of identifying patients and initiating antiretroviral therapy while their immune function is still competent, compared with the costs and survival benefits associated with starting care late, on

presentation of an opportunistic infection—as is currently the norm in LMICs.

**Drug Resistance.** Drug resistance occurs as the virus evolves to escape the inhibitory effects of antiretroviral drugs. The capacity of HIV to mutate is extraordinary, as the wide diversity of HIV variants that occurs worldwide demonstrates. Viral diversification is driven by low-fidelity enzymes (which have a high rate of mutation) that carry out replication of the viral genome.

Drug resistance resulting from being infected by a drug-resistant HIV strain is known as primary drug resistance. Secondary drug resistance develops as a consequence of treatment. Primary HIV drug resistance to nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors has been reported (Salomon and others 2000; Wegner and others 2000). The first reports of transmission of drug resistance have typically occurred within a few years of a drug's introduction into clinical practice. The proportion of newly infected people who acquire drug-resistant HIV has implications for the choice of first-line regimen. Primary resistance in recently infected individuals in high-income countries is stable or has been in decline since 2000, following a rise between 1996 and 1999. Almost nothing is known regarding primary drug resistance among those recently infected in low-income countries, although this question will become more important with the increased availability of antiretroviral therapy in resource-limited settings.

Drug resistance is associated with increases in plasma viral RNA levels and attenuation of the responses of CD4 counts to therapy. Nonetheless, clinical and epidemiological observations suggest that drug resistance does not completely offset the benefits of therapy (Deeks and others 1999; Ledergerber and others 1999). Individuals with drug-resistant HIV typically have plasma viral RNA levels that remain 3- to 10-fold lower than pretreatment levels. Furthermore, patients with drug resistance experience more rapid immunological decline and disease progression if they discontinue their drugs (Nijhuis, Deeks, and Boucher 2001).

**Importance of Adherence to Prescribed Therapy.** With certain drugs, resistance can develop in as little as two weeks if therapy is suboptimal (which can be less than 90 percent adherence). Conversely, patients who adhere to therapy can obtain continued viral suppression for many years without the need for second- or third-line options. Research has shown that drug adherence is one of the most important predictors of continued treatment response (Mannheimer and others 2002). Patients in resource-limited countries are likely to be subjected to a number of influences that challenge their

ability to adhere to the prescribed therapy, including limited education and the consequent poorer understanding of their disease state, unstable housing and financial circumstances, a limited number of treatment options, and clinicians with limited antiretroviral therapy treatment experience (Kitahata and others 1996). Those factors, in addition to the toxicity of the therapy, influence adherence and future disease progression rates (Duran and others 2001) and lead to an increase in drug resistance. Thus, poorly coordinated scale-up of antiretroviral therapy in some developing countries has the potential to jeopardize both the duration of clinical benefit for the first wave of patients who receive substandard care and future response rates as the prevalence of drug resistance increases (Harries and others 2001).

Studies in India, Mexico, Senegal, and Uganda point to poor adherence (which for some classes of drugs can be adherence of less than 95 percent), inadequate doses and regimens, and poor monitoring as factors that contribute to more rapid development of antiretroviral therapy resistance (Oyugi and Bangsberg 2004, Laniece and others 2004, Bautista and others 2003, Liechty and Bangsberg 2003). By contrast, experiences in Haiti and Uganda suggest that it is possible to achieve adherence rates in developing countries equal to or better than those observed in high-income countries (Farmer and others 2001; Mitty and others 2002).

**Second-Line and Subsequent Therapies.** Studies from high-income countries have unequivocally demonstrated that the probability that an antiretroviral therapy regimen will achieve viral suppression diminishes with each subsequent regimen (Deeks and others 1999). Similarly, the mean duration of viral suppression for those who achieve suppression is also lower for subsequent regimens (Deeks and others 1999). This finding is entirely expected because failing a previous regimen is associated with lower adherence, higher toxicity, or side effects and increased resistance, all of which increase the probability of similar problems occurring with subsequent regimens. Thus, the expected survival benefit per month of antiretroviral therapy declines with each change of regimen. In contrast, the monthly cost of therapy rises as a patient moves from first-line to more expensive protease inhibitor-based second-line and subsequent therapies. Given this steadily declining cost-effectiveness, wealthier countries are likely to offer a greater number of regimen changes than poorer countries.

### **Laboratory Monitoring of Immune Function to Guide Therapy**

Laboratory monitoring determines when antiretroviral therapy should be initiated and when it should be changed because of toxicity, lack of efficacy, or resistance. The optimal frequency

and precision of monitoring depends on numerous factors, principally the following:

- the expected rate of change of variables of interest
- the expected frequency of events, such as development of resistance, adherence failure, and side effects
- the relative cost of monitoring versus the cost of providing ineffective treatment
- the magnitude of the secondary effects of monitoring (motivating prevention, motivating adherence).

WHO has suggested a pragmatic approach to monitoring, with inexpensive, easy-to-measure parameters (bodyweight or body mass index, body temperature, hemoglobin, liver enzymes, and clinical symptoms) for monitoring in low-income countries. More specialized markers—namely, CD4 count, viral load, and resistance genotyping—would be restricted to sentinel sites and tertiary care services (Gutierrez and others 2004), at least initially.

The large price reductions for antiretroviral drugs are only now starting to be mirrored in the costs of monitoring tests as new technologies are introduced, collective bargaining is undertaken, and international pressure mounts on diagnostic manufacturers to provide more favorable pricing for LMICs. Commercial cytometric CD4 measurements are now available to some developing countries at less than US\$5 per test (R. Göhde, personal communication, 2004). Viral load testing is still significantly more expensive, but even those prices have dropped to US\$20 following negotiations on behalf of low-income countries by the William Jefferson Clinton Foundation. Even when the potential savings become an operational reality in developing countries, the costs of laboratory monitoring will still represent an important proportion of the costs of providing antiretroviral therapy.

**Monitoring to Guide Initiation of Antiretroviral Therapy.** If laboratory monitoring is performed, its optimal frequency must be determined. The closer patients get to an antiretroviral therapy threshold, the more often they must be tested to detect a CD4 decline that falls within a specific CD4 range. As use of antiretroviral therapy expands in LMICs and as the costs of drugs fall relative to the costs of laboratory monitoring, collecting empirical data and constructing models to compare different monitoring strategies is becoming increasingly urgent.

In the absence of capacity to perform CD4 counts, several studies suggest that total lymphocyte count can be used as a proxy because of the correlation between the two counts (Badri and Wood 2003). Research has also shown that falling body mass index is highly predictive of disease progression (Pistone and others 2002). In light of those findings, the cost-effectiveness of CD4 monitoring in developing countries must be considered in terms of its incremental improvement over total lymphocyte

monitoring or body mass index monitoring rather than being compared with no monitoring at all.

**Testing for Primary Resistance.** Testing for resistance in individual patients is still costly, because of both the cost of the diagnostic kit and the sophisticated laboratory capacity required to perform the tests. Because primary resistance is far less prevalent in LMICs than in high-income countries, no serious consideration is being given at this time to initiating individual resistance testing in the developing world. However, the choice of optimal first-line and subsequent treatment strategies should be guided by information about the prevalence of primary resistance to different antiretroviral drugs in a particular country, which indicates that population-level monitoring of the prevalence of resistance among antiretroviral-naïve people living with HIV/AIDS is important.

**Monitoring Response to Therapy.** Ideally, therapeutic failure should be detected as soon as possible to permit the implementation of clinical strategies to address toxicity, drug resistance, or poor adherence. Therapeutic failure leads to rising viral load and falling immune competence and to the subsequent development of opportunistic infections. Unfortunately, earlier detection comes at a price: testing for increases in viral load, which can be detected soonest, is more expensive than CD4 testing, which in turn is more expensive than the less sensitive monitoring of total lymphocyte count, which is more expensive than monitoring body mass index or waiting until clinical signs of failure appear. Where facilities for detecting early failure are absent, first-line therapy should be replaced by a completely new combination at failure, usually a protease inhibitor-based combination.

**Monitoring Toxicity.** Available antiretroviral drugs have significant toxicity. Such toxicity is often insidious, progressing unnoticed until the patient's health has been seriously impaired. Examples include zidovudine-associated anemia, nevirapine-associated impaired liver function, and didanosine-associated pancreatitis. Fortunately, the most commonly encountered serious toxicities can be detected either on clinical examination or with inexpensive laboratory tests. Data on the relative cost-effectiveness of different toxicity monitoring regimens are unavailable. Current guidelines identify what monitoring should be conducted in conjunction with specific antiretroviral drugs, depending on whether laboratory capacity is available (WHO 2004).

Unfortunately, in the absence of a quantitative analysis of the costs of monitoring and the benefits associated with early detection of toxicity, it is difficult to provide guidance on the minimum laboratory capacity that should accompany the delivery of specific treatment combinations. Clearly, extremely low-cost monitoring tests are warranted for toxicities that

occur frequently. The preeminent example is anemia monitoring for patients receiving zidovudine. Hemoglobin levels can be monitored for less than US\$0.02 per test, which is almost certainly cost-effective given that the incidence of anemia with zidovudine therapy is approximately 10 percent in advanced-stage patients and that anemia frequently progresses to life-threatening levels if not detected.

## RESEARCH AGENDA

As in many other areas of public health in developing countries, a profound tension exists between (a) the need for research to discover new technologies and interventions for both prevention and care and (b) the need for research to learn how to effectively apply the technologies that are currently available. The most important barrier to control is lack of

### Box 18.7

#### Interventions in the Pipeline or in Trial

The following interventions are currently being developed or evaluated:

- *Microbicides.* Most microbicide products are currently in preclinical development; however, 18 products are being evaluated in clinical research studies, most in small phase 1 safety and acceptability trials. Three phase 3 effectiveness trials are currently under way.
- *Diaphragms.* The safety and effectiveness of the diaphragm and Replens gel in preventing HIV and STIs among women are being tested in an ongoing phase 3 randomized controlled trial in South Africa and Zimbabwe. Two trials, in the Dominican Republic and Madagascar, are planned to test the diaphragm's effectiveness against bacterial STIs. Several other trials in Sub-Saharan Africa are planned to test the acceptability and safety of the diaphragms plus microbicides.
- *Circumcision.* Two randomized controlled trials are under way in Kenya and Uganda to examine whether circumcision confers protection among adult men.
- *Community-based VCT.* Project Accept is a community-based VCT trial in 32 communities in South Africa, Tanzania, and Zimbabwe and 14 communities in Thailand. Communities are randomized to receive either a community-based VCT intervention or a standard clinic-based VCT. The community-based VCT intervention has three major strategies: to make VCT more available in community settings, to engage the community through outreach, and to provide posttest support.
- *HSV-2 treatment.* One study in six countries will determine the efficacy of twice-daily acyclovir in reducing susceptibility to HIV infection among high-risk, HIV-negative, HSV-2 seropositive women and men who have sex with men. A companion study will also be

conducted to assess whether acyclovir reduces HIV infectiousness in individuals infected with both HSV-2 and HIV.

- *Tenofovir for preexposure use.* Studies are now enrolling participants at three West African sites and will soon begin in Botswana, Malawi, Thailand, and the United States.
- *Antiretroviral therapy to prevent sexual transmission.* A phase 3, randomized, controlled, multisite trial to assess whether antiretroviral therapy can prevent sexual transmission of HIV in serodiscordant couples will begin in Brazil, India, Malawi, Thailand, and Zimbabwe.
- *Vaccines.* Although preliminary results from a phase 3 clinical trial in Thailand found that AIDSVAX failed to protect against infection, several other vaccines are being developed. Merck and GlaxoSmithKline have unveiled sizable vaccine programs and moved products into human testing. An International AIDS Vaccine Initiative U.K.-Kenya team is in the midst of intermediate human trials of DNA/MVA (modified vaccinia virus Ankara), and Aventis Pasteur is taking ALVAC-AIDSVAX into the final phase of trials. The South African AIDS Vaccine Initiative is preparing for the country's first trials, India's prime minister has pledged national resources for vaccines, and the European Union is broadening its vaccine research for HIV.
- *Behavior change programs for people with HIV.* In recent years, a growing number of public health experts have proposed implementing prevention interventions that target people with HIV (De Cock, Marum, and Mbori-Ngacha 2003; Janssen and others 2001), although evidence on the most effective strategies to encourage safer behavior among people with HIV is lacking.

Source: Authors.

knowledge about how best to implement packages of existing interventions at the appropriate scale to maximize the effect of prevention and care interventions and to protect the human rights of those affected by the epidemic. Accurate surveillance data are needed on risk behaviors, and effectiveness research is needed to discern what interventions work where and how they do so. Unfortunately, few rigorous evaluations of new or existing interventions have been conducted using large prospective cohorts, with the result that, for many interventions, convincing data on effectiveness are not available. Finally, research on policy or structural interventions, which by definition must be conducted on a population level, is also insufficient. These interventions include the development and testing of such policy tools as changing the tax structure, regulating the sex industry, and guaranteeing property rights and access to credit for women.

Box 18.7 lists new prevention interventions in the pipeline. Although numerous promising interventions are listed, results for most of these strategies are at best years away. Centuries hence, when future generations study the history of our time and the epidemic that killed 50 million or perhaps many more, the most difficult question to answer may well be “why did they invest so little for so long in developing a vaccine?” Creating such knowledge is about as close as one can get to a pure international public good, and the lack of global cooperation in adequately funding such research is an indictment of global commitment to multilateral cooperation. However, given both the uncertainty about whether developing an effective vaccine is possible and the long delay until a new vaccine can be widely applied, vaccine development efforts must be accompanied by the development of other new biomedical and behavioral prevention technologies.

In contrast, research on care and treatment has been far more successful than research on prevention, and innovation in new therapies continues apace. The ability of HIV to rapidly evolve resistance to antiretroviral drugs, combined with the existence of an important market in high- and middle-income countries, appears to ensure continued investment in new drug development. In addition, because treatment generally has important commercial returns, HIV therapies, unlike behavioral interventions, have benefited the most from private sector investment. The paradox is that research on the behavioral aspects of adherence to drug regimens would improve the effectiveness of antiretroviral therapy, and thereby benefit both commercial and public interests.

The greatest research challenges in relation to care and treatment in developing countries do not revolve around new drug development. They revolve around how to adapt care and treatment strategies to low-income, low-technology, low-human resource capacity settings in ways that maximize adherence; minimize toxicity, monitoring, and costs; and maximize

the prolongation of high-quality life from antiretroviral therapy—all without damaging existing and often fragile health care infrastructure that must also address other health concerns. Although simplified regimens, such as delivering multiple drugs in a single tablet and fewer doses per day, are desirable everywhere, they are especially important in low-resource settings. Similarly, low-technology, low-cost monitoring tests for antiretroviral therapy toxicity and for immunological and virological responses to treatment are especially needed in low-income countries, which otherwise must centralize testing—an especially difficult prospect when transport and communications systems are poorly developed.

## CONCLUSION

Despite the glaring deficits in AIDS research, the magnitude and seriousness of the global pandemic calls for action in the absence of definitive data. The appropriate mix and distribution of prevention and treatment interventions depends on the stage of the epidemic in a given country and the context in which it occurs. In the absence of firm data to guide program objectives, national strategies may not accurately reflect the priorities dictated by the particular epidemic profile, resulting in highly inefficient investments in HIV/AIDS prevention and care. This waste undoubtedly exacerbates funding shortfalls and results in unnecessary HIV infections and premature deaths. The lack of good data—and thus the ability to tailor responses to epidemics—may be somewhat understandable when the burden of disease is minimal and the resources dedicated to it are similarly small. Neither is the case for HIV/AIDS.

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## NOTE

1. See <http://www.hivinsite.org/global?page=cr-00-04> for a compilation of international guidelines.

## BIBLIOGRAPHY

- Agha, S., A. Karlyn, and D. Meekers. 2001. "The Promotion of Condom Use in Non-Regular Sexual Partnerships in Urban Mozambique." *Health Policy and Planning* 16 (2): 144–51.
- Alcades, P., A. Munoz, D. Vlahov, and G. H. Friedland. 1993. "Incubation Period of Human Immunodeficiency Virus." *Epidemiologic Reviews* 15 (2): 303–18.
- Anthony, J. C., D. Vlahov, K. E. Nelson, S. Cohn, J. Astemborski, and L. Solomon. 1991. "New Evidence on Intravenous Cocaine Use and the Risk of Infection with Human Immunodeficiency Virus Type 1." *American Journal of Epidemiology* 134: 1175–89.
- Anzala, O. A., N. J. Nagelkerke, J. Bwayo, D. Holton, S. Moses, and E. Ngugi. 1995. "Rapid Progression to Disease in African Sex Workers with Human Immunodeficiency Virus Type 1 Infection." *Journal of Infectious Diseases* 171 (3): 686–89.
- Askew, I., and M. Berer. 2003. "The Contribution of Sexual and Reproductive Health Services to the Fight against HIV/AIDS: A Review." *Reproductive Health Matters* 11 (22): 51–73.
- Auvert, B., A. Buve, E. Lagarde, M. Kahindo, J. Chege, N. Rutenberg, and others. 2001. "Male Circumcision and HIV Infection in Four Cities in Sub-Saharan Africa." *AIDS* 15 (Suppl. 4): S31–40.
- Auvert, B., A. Puren, D. Taljaard, E. Lagarde, R. Sitta, and J. Tambekou. 2005. "Impact of Male Circumcision on the Female-to-Male Transmission of HIV." Paper presented at the 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, July 24–27.
- Ayouba, A., G. Tene, P. Cunin, Y. Foupouapouognigni, E. Menu, A. Kfutwah, and others. 2003. "Low Rate of Mother-to-Child Transmission of HIV-1 after Nevirapine Intervention in a Pilot Public Health Program in Yaounde, Cameroon." *Journal of Acquired Immune Deficiency Syndrome* 34 (3): 274–80.
- Bacellar, H., A. Munoz, E. N. Miller, B. A. Cohen, D. Besley, O. A. Selnes, and others. 1994. "Incidence of Clinical AIDS Conditions in a Cohort of Homosexual Men with CD4+ Cell Counts <100/mm<sup>3</sup>: Multicenter AIDS Cohort Study." *Journal of Infectious Diseases* 170 (5): 1284–87.
- Badri, M., and R. Wood. 2003. "Usefulness of Total Lymphocyte Count in Monitoring Highly Active Antiretroviral Therapy in Resource-Limited Settings." *AIDS* 17 (4): 541–45.
- Basu, I., S. Jana, M. J. Rotheram-Borus, D. Swendeman, S. J. Lee, P. Newman, and R. Weiss. 2004. "HIV Prevention among Sex Workers in India." *Journal of Acquired Immune Deficiency Syndrome* 36 (3): 845–52.
- Bautista, S., T. Dmytraczenko, G. Kombe, and S. Bertozzi. 2003. Costing of HIV/AIDS Treatment in Mexico. In *Technical Report No. 020*. Edited by Project PHRplus. Bethesda, MD: Abt Associates, Inc.
- Bell, J. C., D. N. Rose, and H. S. Sacks. 1999. "Tuberculosis Preventive Therapy for HIV-Infected People in Sub-Saharan Africa Is Cost-Effective." *AIDS* 13 (12): 1549–56.
- Bentley, M. E., K. Spratt, M. E. Shepherd, R. R. Gangakhedkar, S. Thilikavathi, R. C. Bollinger, and S. M. Mehendale. 1998. "HIV Testing and Counseling among Men Attending Sexually Transmitted Disease Clinics in Pune, India: Changes in Condom Use and Sexual Behavior over Time." *AIDS* 12 (14): 1869–77.
- Berenguer, J., F. Laguna, J. Lopez-Aldeguer, S. Moreno, J. R. Arribas, J. Arrizabalaga, and others. 2004. "Prevention of Opportunistic Infections in Adult and Adolescent Patients with HIV Infection: GESIDA/National AIDS Plan Guidelines, 2004." *Enfermedades Infecciosas y Microbiologia Clinica* 22 (3): 160–76.
- Bertozzi, S. M., N. S. Padian, J. Wegbreit, B. Feldman, L. DeMaria, H. Gayle, and others. Forthcoming. "HIV/AIDS Prevention and Treatment." Disease Control Priorities Project Working Paper 39, Bethesda, MD. <http://www.fic.nih.gov/dccp/wps.html>.
- Bhave, G., C. P. Lindan, E. S. Hudes, S. Desai, U. Wagle, S. P. Tripathi, and J. S. Mandel. 1995. "Impact of an Intervention on HIV, Sexually Transmitted Diseases, and Condom Use among Sex Workers in Bombay, India." *AIDS* 9 (Suppl. 1): S21–30.
- Bobrik, A. 2004. "HIV Prevention among IDUs in Russia: A Cost-Effectiveness Analysis." Paper presented at the 14th International Conference on the Reduction of Drug-Related Harm, April, Chiang Mai, Thailand.
- Bonnard, P. 2002. "HIV/AIDS Mitigation Using What We Already Know." Technical Note 5, Food and Nutrition Technical Assistance (FANTA) Project, Washington, DC.
- Buve, A. 2002. "HIV Epidemics in Africa: What Explains the Variations in HIV Prevalence?" *International Union of Biochemistry and Molecular Biology Life* 53 (4–5): 193–95.
- Cardo, D. M., D. H. Culver, C. A. Ciesielski, P. U. Srivastava, R. Marcus, D. Abiteboul, and others. 1997. "A Case-Control Study of HIV Seroconversion in Health Care Workers after Percutaneous Exposure." Centers for Disease Control and Prevention Needlestick Surveillance Group. *New England Journal of Medicine* 337 (21): 1485–90.
- Carlisle, D. 2003. "Africans Are Dying of AIDS without Pain Relief." *British Medical Journal* 327 (7423): 1069.
- Carre, N., C. Deveau, F. Belanger, F. Boufassa, A. Persoz, C. Jadand, and others. 1994. "Effect of Age and Exposure Group on the Onset of AIDS in Heterosexual and Homosexual HIV-infected Patients: SEROCO Study Group." *AIDS* 8 (6): 797–802.
- Castro, A., and P. Farmer. 2005. "Understanding and Addressing AIDS-Related Stigma: From Anthropological Theory to Clinical Practice in Haiti." *American Journal of Public Health* 95 (1): 53–59.
- Cates, W. 2004. "A Funny Thing Happened on the Way to FHI." *Sexually Transmitted Diseases* 31 (1): 3–7.
- CDC (U.S. Centers for Disease Control and Prevention). 1989. *Guidelines for the Prevention of HIV and Hepatitis B*. Atlanta: CDC.
- Celentano, D. D., K. C. Bond, C. M. Lyles, S. Eiumtrakul, V. F. Go, C. Beyrer, and others. 2000. "Preventive Intervention to Reduce Sexually Transmitted Infections: A Field Trial in the Royal Thai Army." *Archives of Internal Medicine* 160 (4): 535–40.
- Chaisson, R. E., P. Bacchetti, D. Osmond, B. Brodie, M. A. Sande, and A. R. Moss. 1989. "Cocaine Use and HIV Infection in Intravenous Drug Users in San Francisco." *Journal of the American Medical Association* 261 (4): 561–65.
- CHI (Center for HIV Information). 2005. "HIV Insite." University of California, San Francisco. <http://hivinsite.org>.
- Colebunders, R. L., and A. S. Latif. 1991. "Natural History and Clinical Presentation of HIV-1 Infection in Adults." *AIDS* 5 (Suppl. 1): S103–12.
- Connor, E. M., R. S. Sperling, R. Gelber, P. Kiselev, G. Scott, M. J. O'Sullivan, and others. 1994. "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment." Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 331 (18): 1173–80.
- Cook, J. A., D. Grey, J. Burke, M. H. Cohen, A. C. Gurtman, J. L. Richardson, and others. 2004. "Depressive Symptoms and AIDS-Related Mortality among a Multisite Cohort of HIV-Positive Women." *American Journal of Public Health* 94 (7): 1133–40.
- Coutsoudis, A. 2002. "Breastfeeding and HIV Transmission." In *Public Health Issues in Infant and Child Nutrition*, vol. 48, ed. R. E. Black and K. F. Michaelsen. Nestle Nutrition Workshop Series. Philadelphia: Lippincott Williams & Wilkins.
- Coutsoudis, A., K. Pillay, L. Kuhn, E. Spooner, W. Y. Tsai, and H. M. Coovadia. 2001. "Method of Feeding and Transmission of HIV-1 from Mothers to Children by 15 Months of Age: Prospective Cohort Study from Durban, South Africa." *AIDS* 15 (3): 379–87.

- Coutsoudis, A., K. Pillay, E. Spooner, L. Kuhn, and H. M. Coovadia. 1999. "Influence of Infant-Feeding Patterns on Early Mother-to-Child Transmission of HIV-1 in Durban, South Africa: A Prospective Cohort Study." *South African Vitamin A Study Group. Lancet* 354 (9177): 471–76.
- Creese, A., K. Floyd, A. Alban, and L. Guinness. 2002. "Cost-Effectiveness of HIV/AIDS Interventions in Africa: A Systematic Review of the Evidence." *Lancet* 359 (9318): 1635–43.
- Dabis, F., P. Msellati, N. Meda, C. Wellfens-Ekra, B. You, O. Manigart, and others. 1999. "6-Month Efficacy, Tolerance, and Acceptability of a Short Regimen of Oral Zidovudine to Reduce Vertical Transmission of HIV in Breastfed Children in Côte d'Ivoire and Burkina Faso: A Double-Blind Placebo-Controlled Multicentre Trial." DITRAME Study Group. *Lancet* 353 (9155): 786–92.
- De Cock, K. M., E. Marum, and D. Mbori-Ngacha. 2003. "A Serostatus-Based Approach to HIV/AIDS Prevention and Care in Africa." *Lancet* 362 (9398): 1847–49.
- Deeks, S. G., J. D. Barbour, J. N. Martin, M. S. Swanson, and R. M. Grant. 2000. "Sustained CD4+ T Cell Response after Virologic Failure of Protease Inhibitor-Based Regimens in Patients with Human Immunodeficiency Virus Infection." *Journal of Infectious Diseases* 181 (3): 946–53.
- Deeks, S. G., F. M. Hecht, M. Swanson, T. Elbeik, R. Loftus, P. T. Cohen, and others. 1999. "HIV RNA and CD4 Cell Count Response to Protease Inhibitor Therapy in an Urban AIDS Clinic: Response to Both Initial and Salvage Therapy." *AIDS* 13 (6): F35–43.
- DeGruttola, V., G. R. Seage, K. H. Mayer, C. R. Horsburgh. 1989. "Infectiousness of HIV between Male Homosexual Partners." *Journal of Clinical Epidemiology* 42 (9): 849–56.
- Des Jarlais, D. C., and S. R. Friedman. 1996. "HIV Epidemiology and Interventions among Injecting Drug Users." *International Journal of Sexually Transmitted Diseases and AIDS* 7 (Suppl. 2): 57–61.
- Deschamps, M. M., J. W. Pape, A. Hafner, and W. D. Johnson. 1996. "Heterosexual Transmission of HIV in Haiti." *Annals of Internal Medicine* 125 (4): 324–30.
- Donnelly, J. 2004. "Circumcised Men Less Likely to Get AIDS." *Boston Globe*, November 16.
- Duran, S., M. Saves, B. Spire, V. Cailleton, A. Sobel, P. Carrieri, and others. 2001. "Failure to Maintain Long-Term Adherence to Highly Active Antiretroviral Therapy: The Role of Lipodystrophy." *AIDS* 15 (18): 2441–44.
- Dziank, G., D. Chisholm, B. Johns, J. Rovira, and Y. J. Hutin. 2003. "The Cost-Effectiveness of Policies for the Safe and Appropriate Use of Injection in Healthcare Settings." *Bulletin of the World Health Organization* 81 (4): 277–85.
- Easterbrook, P. J. 1994. "Non-Progression in HIV Infection." *AIDS* 8 (8): 1179–82.
- Egger, M., J. Pauw, A. Lopatzidiz, D. Medrano, F. Paccaud, and G. D. Smith. 2000. "Promotion of Condom Use in a High-Risk Setting in Nicaragua: A Randomised Controlled Trial." *Lancet* 355 (9221): 2101–05.
- Eshleman, S. H., M. Mraçna, L. A. Guay, M. Deseyve, S. Cunningham, M. Mirochnick, and others. 2001. "Selection and Fading of Resistance Mutations in Women and Infants Receiving Nevirapine to Prevent HIV-1 Vertical Transmission (HIVNET 012)." *AIDS* 15 (15): 1951–57.
- Farmer, P., F. Leandre, J. Mukherjee, R. Gupta, L. Tarter, and J. Y. Kim. 2001. "Community-Based Treatment of Advanced HIV Disease: Introducing DOT-HAART (Directly Observed Therapy with Highly Active Antiretroviral Therapy)." *Bulletin of the World Health Organization* 79 (12): 1145–51.
- Fawole, I. O., M. C. Asuzu, S. O. Oduntan, and W. R. Brieger. 1999. "A School-Based AIDS Education Programme for Secondary School Students in Nigeria: A Review of Effectiveness." *Health Education Resources* 14 (5): 675–83.
- Fawzi, W., G. Msamanga, G. Antelman, C. Xu, E. Hertzmark, D. Spiegelman, and others. 2004. "Effect of Prenatal Vitamin Supplementation on Lower-Genital Levels of HIV Type 1 and Interleukin Type 1 Beta at 36 Weeks of Gestation." *Clinical Infectious Diseases* 38 (5): 716–22.
- Feachem, R. G. 2004. "The Research Imperative: Fighting AIDS, TB, and Malaria." *Tropical Medicine and International Health* 9 (11): 1139–41.
- Fleming, T. R., and D. L. DeMets. 1996. "Surrogate End Points in Clinical Trials: Are We Being Misled?" *Annals of Internal Medicine* 125: 605–13.
- Floyd, K., D. Wilkinson, and C. Gilks. 1997. "Comparison of Cost Effectiveness of Directly Observed Treatment (DOT) and Conventionally Delivered Treatment for Tuberculosis: Experience from Rural South Africa." *British Medical Journal* 315 (7120): 1407–11.
- Ford, K., D. N. Wirawan, P. Fajans, P. Meliawan, K. MacDonald, and L. Thorpe. 1996. "Behavioral Interventions for Reduction of Sexually Transmitted Disease/HIV Transmission among Female Commercial Sex Workers and Clients in Bali, Indonesia." *AIDS* 10 (2): 213–22.
- Foster, S., and A. Buve. 1995. "Benefits of HIV Screening of Blood Transfusions in Zambia." *Lancet* 346 (8969): 225–27.
- Garcia, P. M., L. A. Kalish, J. Pitt, H. Minkoff, T. C. Quinn, S. K. Burchett, and others. 1999. "Maternal Levels of Plasma Human Immunodeficiency Virus Type 1 RNA and the Risk of Perinatal Transmission. Women and Infants Transmission Study Group." *New England Journal of Medicine* 341 (6): 394–402.
- Ghys, P. D., M. O. Diallo, V. Ettiegné-Traore, K. Kale, O. Tawil, M. Carael, and others. 2002. "Increase in Condom Use and Decline in HIV and Sexually Transmitted Diseases among Female Sex Workers in Abidjan, Côte d'Ivoire, 1991–1998." *AIDS* 16 (2): 251–58.
- Gillespie, S., L. Haddad, and R. Jackson. 2001. "HIV/AIDS Food and Nutrition Security: Impacts and Actions." Paper prepared for the 29th Session of the ACC/SCN Symposium on Nutrition and HIV/AIDS.
- Gilson, L., R. Mkanje, H. Grosskurth, F. Mosha, J. Picard, A. Gavyole, and others. 1997. "Cost-Effectiveness of Improved Treatment Services for Sexually Transmitted Diseases in Preventing HIV-1 Infection in Mwanza Region, Tanzania." *Lancet* 350 (9094): 1805–9.
- Gisselquist, D., J. J. Potterat, R. Rothenberg, E. M. Drucker, S. Brody, D. Brewé, and others. 2003. "Examining the Hypothesis That Sexual Transmission Drives Africa's HIV Epidemic." *AIDScience* 3 (10). <http://www.aids-science.org/Articles/AIDScience032.asp>.
- Global HIV Prevention Working Group. 2003. *Access to HIV Prevention—Closing the Gap*. Menlo Park, CA: Kaiser Family Foundation.
- Göhde, R. 2004. Personal Communication. HIV/AIDS Project Coordinator, Münster, Germany.
- Goldie, S. J., L. Kuhn, L. Denny, A. Pollack, and T. C. Wright. 2001. "Policy Analysis of Cervical Cancer Screening Strategies in Low-Resource Settings: Clinical Benefits and Cost-Effectiveness." *Journal of the American Medical Association* 285 (24): 3107–15.
- Grant, R. M., F. M. Hecht, M. Warmerdam, L. Liu, T. Liegler, C. J. Petropoulos, and others. 2002. "Time Trends in Primary HIV-1 Drug Resistance among Recently Infected Persons." *Journal of the American Medical Association* 288 (2): 181–88.
- Grant, R. M., J. Kahn, M. Warmerdam, L. Liu, C. J. Petropoulos, N. S. Hellman, and F. Hecht. 2002. "Transmission and Transmissibility of Drug Resistant HIV-1 (368-M)." Paper presented at 9th Conference on Retroviruses and Opportunistic Infections, Seattle, February 24–28.
- Grassly, N. C., G. P. Garnett, B. Schwartlander, S. Gregson, and R. M. Anderson. 2001. "The Effectiveness of HIV Prevention and the Epidemiological Context." *Bulletin of the World Health Organization* 79 (12): 1121–32.
- Gregson, S., P. R. Mason, G. P. Garnett, T. Zhuwau, C. A. Nyamukapa, R. M. Anderson, and S. K. Chandiwana. 2001. "A Rural HIV Epidemic in Zimbabwe? Findings from a Population-Based Survey."

- International Journal of Sexually Transmitted Diseases and AIDS* 12 (3): 189–96.
- Grosskurth, H., F. Mosha, J. Todd, E. Mwijarubi, A. Klokke, K. Senkoro, and others. 1995. "Impact of Improved Treatment of Sexually Transmitted Diseases on HIV Infection in Rural Tanzania: Randomised Controlled Trial." *Lancet* 346 (8974): 530–36.
- Guay, L. A., P. Musoke, T. Fleming, D. Bagenda, M. Allen, C. Nakabiito, and others. 1999. "Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: HIVNET 012 Randomised Trial." *Lancet* 354 (9181): 795–802.
- Gutierrez, J. P., B. Johns, T. Adam, S. M. Bertozzi, T. T. Edejer, R. Greener, and others. 2004. "Achieving the WHO/UNAIDS Antiretroviral Treatment 3 by 5 Goal: What Will It Cost?" *Lancet* 364 (9428): 63–64.
- Hammer, S. M., K. E. Squires, M. D. Hughes, J. M. Grimes, L. M. Demeter, J. S. Currier, and others. 1997. "A Controlled Trial of Two Nucleoside Analogues Plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 Per Cubic Millimeter or Less." *New England Journal of Medicine* 337 (11): 725–33.
- Hansen, K., G. Woelk, H. Jackson, R. Kerkhoven, N. Manjonjori, P. Maramba, and others. 1998. "The Cost of Home-Based Care for HIV/AIDS Patients in Zimbabwe." *AIDS Care* 10 (6): 751–59.
- Harries, A. D., D. S. Nyangulu, N. J. Hargreaves, O. Kaluwa, and F. M. Salaniponi. 2001. "Preventing Antiretroviral Anarchy in Sub-Saharan Africa." *Lancet* 358 (9279): 410–14.
- Harvey, B., J. Stuart, and T. Swan. 2000. "Evaluation of a Drama-in-Education Programme to Increase AIDS Awareness in South African High Schools: A Randomized Community Intervention Trial." *International Journal of Sexually Transmitted Diseases and AIDS* 11 (2): 105–11.
- Hayes, R., J. Chagalucha, H. Grosskurth, A. Obasi, J. Todd, B. Cleophas-Mazigr, and others. 2003. "Mema Kwa Vijana: A Randomised Controlled Trial of an Adolescents Sexual and Reproductive Health Intervention Programme in Rural Mwanza, Tanzania: 2 Intervention and Process Indicators." Paper presented at the International Society of Sexually Transmitted Diseases Research Congress, Ottawa, July 27–30.
- Henderson, D. K., B. J. Fahey, M. Will, J. M. Schmitt, K. Carey, D. E. Koziol, and others. 1990. "Risk for Occupational Transmission of Human Immunodeficiency Virus Type 1 (HIV-1) Associated with Clinical Exposures: A Prospective Evaluation." *Annals of Internal Medicine* 113 (1): 740–46.
- Higginson, I. J., I. G. Findlay, D. M. Goodwin, K. Hood, A. G. Edwards, A. Cook, and others. 2003. "Is There Evidence That Palliative Care Teams Alter End-of-Life Experiences of Patients and Their Caregivers?" *Journal of Pain and Symptom Management* 25 (2): 150–168.
- Hira, S. K., G. J. Dore, and T. Sirisanthana. 1998. "Clinical Spectrum of HIV/AIDS in the Asia-Pacific Region." *AIDS* 12 (Suppl. B): S145–54.
- Hira, S. K., H. L. Dupont, D. N. Lanjewar, and Y. N. Dholakia. 1998. "Severe Weight Loss: The Predominant Clinical Presentation of Tuberculosis in Patients with HIV Infection in India." *National Medical Journal of India* 11 (6): 256–58.
- Hook, E. W., R. O. Cannon, A. J. Nahmias, F. F. Lee, C. H. Campbell, D. Glasser, and others. 1992. "Herpes Simplex Virus Infection as a Risk Factor for Human Immunodeficiency Virus Infection in Heterosexuals." *Journal of Infectious Diseases* 165 (2): 251–55.
- Hoover, D. R., A. J. Saah, H. Bacellar, J. Phair, R. Detels, R. Anderson, and others. 1993. "Clinical Manifestations of AIDS in the Era of Pneumocystis Prophylaxis: Multicenter AIDS Cohort Study." *New England Journal of Medicine* 329 (26): 1922–26.
- Hurley, S. F., D. J. Jolley, and J. M. Kaldor. 1997. "Effectiveness of Needle-Exchange Programmes for Prevention of HIV Infection." *Lancet* 349 (9068): 1797–800.
- Hutton, G., K. Wyss, and Y. N'Diekhhor. 2003. "Prioritization of Prevention Activities to Combat the Spread of HIV/AIDS in Resource-Constrained Settings: A Cost-Effectiveness Analysis from Chad, Central Africa." *International Journal of Health Planning and Management* 18 (2): 117–36.
- Ippolito, G., V. Puro, and G. De Carli. 1993. "The Risk of Occupational Human Immunodeficiency Virus Infection in Health Care Workers: Italian Multicenter Study." Italian Study Group on Occupational Risk of HIV Infection. *Annals of Internal Medicine* 153 (12): 1451–58.
- Institute of Medicine, ed. 1997. *The Hidden Epidemic: Confronting Sexually Transmitted Diseases*. Washington, DC: National Academy Press.
- Jackson, D. J., J. P. Rakwar, B. A. Richardson, K. Mandaliya, B. H. Chohan, J. J. Bwayo, and others. 1997. "Decreased Incidence of Sexually Transmitted Diseases among Trucking Company Workers in Kenya: Results of a Behavioural Risk-Reduction Programme." *AIDS* 11 (7): 903–09.
- Jackson, J. B., P. Musoke, T. Fleming, L. A. Guay, D. Bagenda, M. Allen, and others. 2003. "Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: 18-Month Follow-up of the HIVNET 012 Randomised Trial." *Lancet* 362 (9387): 859–68.
- Jacobs, B., and A. Mercer. 1999. "Feasibility of Hospital-Based Blood Banking: A Tanzanian Case Study." *Health Policy and Planning* 14 (4): 354–62.
- Janssen, R. S., D. R. Holtgrave, R. O. Valdiserri, M. Shepherd, H. D. Gayle, and K. M. De Cock. 2001. "The Serostatus Approach to Fighting the HIV Epidemic: Prevention Strategies for Infected Individuals." *American Journal of Public Health* 91 (7): 1019–24.
- Jemmott, J. B., L. S. Jemmott, and G. T. Fong. 1998. "Abstinence and Safer Sex: HIV Risk-Reduction for African American Adolescents." *Journal of the American Medical Association* 279 (19): 1529–36.
- Jenkins, C., H. Rahman, T. Saidel, S. Jana, and A. M. Hussain. 2001. "Measuring the Impact of Needle Exchange Programs among Injecting Drug Users through the National Behavioural Surveillance in Bangladesh." *AIDS Education and Prevention* 13 (5): 452–61.
- Jha, P., L. M. E. Vaz, F. Plummer, N. Nagelkerke, B. Willbond, E. Ngugi, and others. 2001. "The Evidence Base for Interventions to Prevent HIV Infection in Low- and Middle-Income Countries." Commission on Macroeconomics and Health Working Paper. WG5: 2. Commission on Macroeconomics and Health, Geneva, Switzerland.
- John, G. C., R. W. Nduati, D. A. Mbori-Ngacha, B. A. Richardson, D. Panteleeff, A. Mwatha, and others. 2001. "Correlates of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV-1) Transmission: Association with Maternal Plasma HIV-1 RNA Load, Genital HIV-1 DNA Shedding, and Breast Infections." *Journal of Infectious Diseases* 183 (2): 206–12.
- John Snow Inc. 2003. Fact Sheets for Diagnostic Tests. [http://deliver.jsi.com/2002/archives/hivaids/test\\_kits/index.cfm](http://deliver.jsi.com/2002/archives/hivaids/test_kits/index.cfm).
- Kagimu, M., E. Marum, F. Wabwire-Mangen, N. Nakyanjo, Y. Walakira, and J. Hogle. 1998. "Evaluation of the Effectiveness of AIDS Health Education Interventions in the Muslim Community in Uganda." *AIDS Education and Prevention* 10 (3): 215–28.
- Kahn, J. G., S. M. Kegeles, R. Hays, and N. Beltzer. 2001. "Cost-Effectiveness of the Mpowerment Project, a Community-Level Intervention for Young Gay Men." *Journal of Acquired Immune Deficiency Syndrome* 27 (5): 482–91.
- Kalichman, S. C., D. Rompa, M. Cage, K. DiFonzo, D. Simpson, J. Austin, and others. 2001. "Effectiveness of an Intervention to Reduce HIV Transmission Risks in HIV-Positive People." *American Journal of Preventive Medicine* 21 (2): 84–92.
- Kamali, A., M. Quigley, J. Nakiyingi, J. Kinsman, J. Kengeya-Kayondo, R. Gopal, and others. 2003. "Syndromic Management of Sexually Transmitted Infections and Behaviour Change Interventions on

- Transmission of HIV-1 in Rural Uganda: A Community Randomised Trial." *Lancet* 361 (9358): 645–52.
- Kamenga, M., R. W. Ryder, M. Jingu, N. Mbuyi, L. Mbu, F. Behets, and others. 1991. "Evidence of Marked Sexual Behavior Change Associated with Low HIV-1 Seroconversion in 149 Married Couples with Discordant HIV-1 Serostatus: Experience at an HIV Counselling Center in Zaire." *AIDS* 5 (1): 61–67.
- Kaplan, E. H., and R. Heimer. 1992. "A Model-Based Estimate of HIV Infection via Needle-Sharing." *Journal of Acquired Immune Deficiency Syndrome* 5 (11): 1116–18.
- Kaplan, J. E., D. L. Hanson, J. L. Jones, and M. S. Dworkin. 2001. "Viral Load as an Independent Risk Factor for Opportunistic Infections in HIV-Infected Adults and Adolescents." *AIDS* 15 (14): 1831–36.
- Kaplan, J. E., H. Masur, and K. K. Holmes. 2002. "Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons—2002: Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America." *Morbidity and Mortality Weekly Report* 51 (RR-8): 1–52.
- Katz, M. H., S. K. Schwarcz, T. A. Kellogg, J. D. Klausner, J. W. Dilley, S. Gibson, and others. 2002. "Impact of Highly Active Antiretroviral Treatment on HIV Seroincidence among Men Who Have Sex with Men: San Francisco." *American Journal of Public Health* 92 (3): 388–94.
- Katzenstein, D. A., W. McFarland, M. Mbizvo, A. S. Latif, R. Machekano, J. Parsonnet, and others. 1998. "Peer Education among Factory Workers in Zimbabwe: Providing a Sustainable HIV Prevention Intervention." Paper presented at the 12th International Conference on AIDS, Geneva, June 28–July 3.
- Kegeles, S. M., R. B. Hays, and T. J. Coates. 1996. "The Mpowerment Project: A Community-Level HIV Prevention Intervention for Young Gay Men." *American Journal of Public Health* 86 (8): 1129–36.
- Kelly, J. A., D. A. Murphy, K. J. Sikkema, T. L. McAuliffe, R. A. Roffman, L. J. Solomon, and others. 1997. "Randomised, Controlled, Community-Level HIV-Prevention Intervention for Sexual-Risk Behaviour among Homosexual Men in U.S. Cities: Community HIV Prevention Research Collaborative." *Lancet* 350 (9090): 1500–5.
- Kim, N., B. Stanton, X. Li, K. Dickersin, and J. Galbraith. 1997. "Effectiveness of the 40 Adolescent AIDS-Risk Reduction Interventions: A Quantitative Review." *Journal of Adolescent Health* 20 (3): 204–15.
- Kirby, D. 1997. *No Easy Answers: Research Findings on Programs to Reduce Teen Pregnancy*. Washington, DC: National Campaign to Prevent Teen Pregnancy.
- . 2001. *Emerging Answers: Research Findings on Programs to Reduce Teen Pregnancy*. Washington, DC: National Campaign to Prevent Teen Pregnancy.
- Kitahata, M. M., T. D. Koepsell, R. A. Deyo, C. L. Maxwell, W. T. Dodge, and E. H. Wagner. 1996. "Physicians' Experience with the Acquired Immunodeficiency Syndrome as a Factor in Patients' Survival." *New England Journal of Medicine* 334: 701–6.
- Komanduri, K. V., M. N. Viswanathan, E. D. Wieder, D. K. Schmidt, B. M. Bredt, M. A. Jacobson, and others. 1998. "Restoration of Cytomegalovirus-Specific CD4+ T-Lymphocyte Responses after Ganciclovir and Highly Active Antiretroviral Therapy in Individuals Infected with HIV-1." *Nature Medicine* 4 (8): 953–56.
- Ksobiech, K. 2003. "A Meta-Analysis of Needle Sharing, Lending, and Borrowing Behaviors of Needle Exchange Program Attendees." *AIDS Education and Prevention* 15 (3): 257–68.
- Kumaranayake, L., P. Mangtani, A. Boupda-Duate, J. C. Fournema Abada, C. Cheta, Z. Njoumeme, and C. Watts. 1998. "Cost-Effectiveness of an HIV/AIDS Peer Education Programme among Commercial Sex Workers (CSW): Results from Cameroon [abstract no. 33592]." Paper presented at the World AIDS Conference, Geneva, June 28–July 3.
- Kumaranayake, L., P. Vickerman, D. Walker, S. Samoshkin, V. Romantsov, Z. Emelyanova, and others. 2004. "The Cost-Effectiveness of HIV Preventive Measures among Injecting Drug Users in Svetlogorsk, Belarus." *Addiction* 99 (12): 1565–76.
- Ladner, J., V. Leroy, P. Hoffman, M. Nyiraziraje, A. De Clercq, P. Van de Perre, and F. Dabis. 1998. "Chorioamnionitis and Pregnancy Outcome in HIV-Infected African Women: Pregnancy and HIV Study Group." *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 18 (3): 293–98.
- Laga, M., M. Alary, N. Nzila, A. T. Manoka, M. Tuliza, F. Behets, and others. 1994. "Condom Promotion, Sexually Transmitted Diseases Treatment, and Declining Incidence of HIV-1 Infection in Female Zairian Sex Workers." *Lancet* 344 (8917): 246–48.
- Laleman, G., K. Magazani, J. H. Perriens, N. Badibanga, N. Kapila, M. Konde, and others. 1992. "Prevention of Blood-borne HIV Transmission Using a Decentralized Approach in Shaba, Zaire." *AIDS* 6 (11): 1353–58.
- Laniece, I., K. Diop, A. Desclaux, K. Sow, M. Ciss, B. Ndiaye, and I. Ndoye. 2004. "Determinants of long-term adherence to antiretroviral drugs among adults followed over four years in Dakar, Senegal." Abstract presented at the XV International AIDS Conference, July 11–16, Bangkok, Thailand.
- Lanjewar, D. N., B. S. Anand, R. Genta, M. B. Maheshwari, M. A. Ansari, S. K. Hira, and others. 1996. "Major Differences in the Spectrum of Gastrointestinal Infections Associated with AIDS in India versus the West: An Autopsy Study." *Clinical Infectious Disease* 23 (3): 482–85.
- Lauby, J. L., P. J. Smith, M. Stark, B. Person, and J. Adams. 2000. "A Community-Level HIV Prevention Intervention for Inner-City Women: Results of the Women and Infants Demonstration Projects." *American Journal of Public Health* 90 (2): 216–22.
- Ledergerber, B., M. Egger, M. Opravil, A. Telenti, B. Hirschel, M. Battegay, and others. 1999. "Clinical Progression and Virological Failure on Highly Active Antiretroviral Therapy in HIV-1 Patients: A Prospective Cohort Study." Swiss HIV Cohort Study. *Lancet* 353 (9156): 863–68.
- Ledergerber, B., A. Mocroft, P. Reiss, H. Furrer, O. Kirk, M. Bickel, and others. 2001. "Discontinuation of Secondary Prophylaxis against *Pneumocystis carinii* Pneumonia in Patients with HIV Infection Who Have a Response to Antiretroviral Therapy: Eight European Study Groups." *New England Journal of Medicine* 344 (3): 168–74.
- Leigh Brown, A. J., S. D. Frost, W. C. Mathews, K. Dawson, N. S. Hellmann, E. S. Daar, and others. 2003. "Transmission Fitness of Drug-Resistant Human Immunodeficiency Virus and the Prevalence of Resistance in the Antiretroviral-Treated Population." *Journal of Infectious Diseases* 187 (4): 683–86.
- Levine, W. C., R. Revollo, V. Kaune, J. Vega, F. Tinajeros, M. Garnica, and others. 1998. "Decline in Sexually Transmitted Disease Prevalence in Female Bolivian Sex Workers: Impact of an HIV Prevention Project." *AIDS* 12 (14): 1899–906.
- Li, T. S., R. Tubiana, C. Katlama, V. Calvez, H. Ait Mohand, and B. Autran. 1998. "Long-Lasting Recovery in CD4 T-Cell Function and Viral-Load Reduction after Highly Active Antiretroviral Therapy in Advanced HIV-1 Disease." *Lancet* 351 (9117): 1682–86.
- Liechty, C. A., and D. R. Bangsberg. 2003. "Doubts about DOT: antiretroviral therapy for resource-poor countries." *AIDS* 17 (9): 1383–1387.
- Little, S. J., S. Holte, J. P. Routy, E. S. Daar, M. Markowitz, A. C. Collier, and others. 2002. "Antiretroviral-Drug Resistance among Patients Recently Infected with HIV." *New England Journal of Medicine* 347 (6): 385–94.
- Low-Beer, D., and R. Stoneburner. 2003. "Behavior and Communication Change in Reducing HIV: Is Uganda Unique?" *African Journal of AIDS Research* 2 (1): 9–21.
- Low-Beer, S., A. E. Weber, K. Bartholomew, M. Landolt, D. Oram, J. S. Montaner, and others. 2000. "A Reality Check: The Cost of Making Post-Exposure Prophylaxis Available to Gay and Bisexual Men at High Sexual Risk." *AIDS* 14 (3): 325–26.

- Lui, K. J., W. W. Darrow, and G. W. Rutherford III. 1988. "A Model-Based Estimate of the Mean Incubation Period for AIDS in Homosexual Men." *Science* 240 (4857): 1333–35.
- Mallal, S. A., M. John, C. B. Moore, I. R. James, and E. J. McKinnon. 2000. "Contribution of Nucleoside Analogue Reverse Transcriptase Inhibitors to Subcutaneous Fat Wasting in Patients with HIV Infection." *AIDS* 14 (10): 1309–16.
- Mannheimer, S., G. Friedland, J. Matts, C. Child, and M. Chesney. 2002. "The Consistency of Adherence to Antiretroviral Therapy Predicts Biologic Outcomes for Human Immunodeficiency Virus-Infected Persons in Clinical Trials." *Clinical Infectious Diseases* 34 (8): 1115–21.
- Marks, G., S. Burris, and T. A. Peterman. 1999. "Reducing Sexual Transmission of HIV from Those Who Know They Are Infected: The Need for Personal and Collective Responsibility." *AIDS* 13 (3): 297–306.
- Marseille, E., P. B. Hofmann, and J. G. Kahn. 2002. "HIV Prevention before HAART in Sub-Saharan Africa." *Lancet* 359 (9320): 1851–56.
- Marseille, E., J. G. Kahn, K. Billingham, and J. Saba. 2001. "Cost-Effectiveness of the Female Condom in Preventing HIV and STDs in Commercial Sex Workers in Rural South Africa." *Social Science and Medicine* 52 (1): 135–48.
- Marseille, E., J. G. Kahn, F. Mmiro, L. Guay, P. Musoke, M. G. Fowler, and others. 1999. "Cost-Effectiveness of Single-Dose Nevirapine Regimen for Mothers and Babies to Decrease Vertical HIV-1 Transmission in Sub-Saharan Africa." *Lancet* 354 (9181): 803–9.
- Marseille, E., J. G. Kahn, and J. Saba. 1998. "Cost-Effectiveness of Antiviral Drug Therapy to Reduce Mother-to-Child HIV Transmission in Sub-Saharan Africa." *AIDS* 12 (8): 939–48.
- Marseille, E., S. F. Morin, C. Collins, T. Summers, T. J. Coates, and J. G. Kahn. 2002. "Cost-Effectiveness of HIV Prevention in Developing Countries." In *HIV InSite Knowledge Base*. <http://hivinsite.ucsf.edu/InSite?page=kb-08-01-04>.
- Martin, H. L., B. A. Richardson, P. M. Nyange, L. Lavreys, S. L. Hillier, B. Chohan, and others. 1999. "Vaginal Lactobacilli, Microbial Flora, and Risk of Human Immunodeficiency Virus Type 1 and Sexually Transmitted Disease Acquisition." *Journal of Infectious Diseases* 180 (6): 1863–68.
- Mast, S. T., J. D. Woolwine, and J. L. Gerberding. 1993. "Efficacy of Gloves in Reducing Blood Volumes Transferred during Simulated Needlestick Injury." *Journal of Infectious Diseases* 168 (6): 1589–92.
- Mastro T. D., G. A. Satten, T. Nopkesorn, S. Sangkharomya, and I. M. Longini. 1994. "Probability of Female-to-Male Transmission of HIV-1 in Thailand." *Lancet* 343 (8891): 204–7.
- Mathers, C. D., A. Lopez, C. Stein, D. Ma Fat, C. Rao, M. Inoue, and others. 2006. "The Burden of Disease and Mortality by Condition: Data, Methods and Results for the Year 2001." In the *Global Burden of Disease in 2001*, ed. A. Lopez, C. Mathers, M. Ezzati, D. Jamison, and C. J. L. Murray. New York: Oxford University Press.
- Mayaud, P., F. Mosha, J. Todd, R. Balira, J. Mgara, B. West, and others. 1997. "Improved Treatment Services Significantly Reduce the Prevalence of Sexually Transmitted Diseases in Rural Tanzania: Results of a Randomized Controlled Trial." *AIDS* 11 (15): 1873–80.
- Mbopi Keou, F. X., G. Gresenguet, P. Mayaud, H. A. Weiss, R. Gopal, D. W. Brown, and others. 1999. "Genital Herpes Simplex Virus Type 2 Shedding Is Increased in HIV-Infected Women in Africa." *AIDS* 13: 536–37.
- McConnell, J., and R. Grant. 2003. "Sorting out Serosorting Using Social Network Methods. Paper presented at the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14.
- McFarland, W., J. G. Kahn, D. A. Katzenstein, D. Mvere, and R. Shamu. 1995. "Deferral of Blood Donors with Risk Factors for HIV Infection Saves Lives and Money in Zimbabwe." *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 9 (2): 183–192.
- McNaghten, A. D., D. L. Hanson, J. L. Jones, M. S. Dworkin, and J. W. Ward. (1999). "Effects of Antiretroviral Therapy and Opportunistic Illness Primary Chemoprophylaxis on Survival after AIDS Diagnosis: Adult/Adolescent Spectrum of Disease Group." *AIDS* 13 (13): 1687–95.
- Meekers, D. 2000. "The Effectiveness of Targeted Social Marketing to Promote Adolescent Reproductive Health: The Case of Soweto, South Africa." *Journal of HIV/AIDS Prevention and Education for Adolescents and Children* 3 (4): 73–92.
- Mesquita, F., D. Doneda, D. Gandolfi, M. I. Nemes, T. Andrade, R. Bueno, and others. 2003. "Brazilian Response to the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Epidemic among Injection Drug Users." *Clinical Infectious Diseases* 37 (Suppl. 5): S382–85.
- Metzger, D. S., H. Navaline, and G. E. Woody. 1998. "Drug Abuse Treatment as AIDS Prevention." *Public Health Reports* 113 (Suppl. 1): 97–106.
- Miotti, P. G., T. E. Taha, N. I. Kumwenda, R. Broadhead, L. A. Mtimavalye, L. Van der Hoeven, and others. 1999. "HIV Transmission through Breastfeeding: A Study in Malawi." *Journal of the American Medical Association* 282 (8): 744–49.
- Mitty, J. A., V. E. Stone, M. Sands, G. Macalino, and T. Flanigan. 2002. "Directly Observed Therapy for the Treatment of People with Human Immunodeficiency Virus Infection: A Work in Progress." *Clinical Infectious Disease* 34 (7): 984–90.
- Morgan, D., G. H. Maude, S. S. Malamba, M. J. Okongo, H. U. Wagner, D. W. Mulder, and others. 1997. "HIV-1 Disease Progression and AIDS-Defining Disorders in Rural Uganda." *Lancet* 350 (9073): 245–50.
- Moses, S., F. A. Plummer, E. N. Ngugi, N. J. Nagelkerke, A. O. Anzala, and J. O. Ndiya-Achola. 1991. "Controlling HIV in Africa: Effectiveness and Cost of an Intervention in a High-Frequency STD Transmitter Core Group." *AIDS* 5 (4): 407–11.
- Munoz, A., C. A. Sabin, and A. N. Phillips. 1997. "The Incubation Period of AIDS." *AIDS* 11 (Suppl. A): S69–76.
- Murphy, D. A., W. D. Marelich, D. Hoffman, and W. N. Steers. 2004. "Predictors of Antiretroviral Adherence." *AIDS Care* 16 (4): 471–84.
- Murray, C. J., E. DeJonghe, H. J. Chum, D. S. Nyangulu, A. Salomao, and K. Styblo. 1991. "Cost-Effectiveness of Chemotherapy for Pulmonary Tuberculosis in Three Sub-Saharan African Countries." *Lancet* 338 (8778): 1305–8.
- Murray, C. J., and A. D. Lopez. 1996. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020*. Boston: Harvard University Press.
- Musicco, M., A. Lazzarin, A. Nicolosi, M. Gasparini, P. Costigliola, C. Arici, and others. 1994. "Antiretroviral Treatment of Men Infected with Human Immunodeficiency Virus Type 1 Reduces the Incidence of Heterosexual Transmission." Italian Study Group on HIV Heterosexual Transmission. *Archives of Internal Medicine* 154 (17): 1971–76.
- Nagachinta, T., A. Duerr, V. Suriyanon, N. Nantachit, S. Rugpao, C. Wanapirak, and others. 1997. "Risk Factors for HIV-1 Transmission from HIV-Seropositive Male Blood Donors to Their Regular Female Partners in Northern Thailand." *AIDS* 11 (14): 1765–72.
- National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. 1998. "Effective Medical Treatment of Opiate Addiction." *Journal of the American Medical Association* 280: 1936–43.
- Nduati, R., G. John, D. Mbori-Ngacha, B. Richardson, J. Overbaugh, A. Mwachira, and others. 2000. "Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: A Randomized Clinical Trial." *Journal of the American Medical Association* 283 (9): 1167–74.
- Nduati, R., B. A. Richardson, G. John, D. Mbori-Ngacha, A. Mwachira, J. Ndiya-Achola, and others. 2001. "Effect of Breastfeeding on

- Mortality among HIV-1 Infected Women: A Randomised Trial." *Lancet* 357 (9269): 1651–55.
- Needle, R. H., S. L. Coyle, J. Normand, E. Lambert, and H. Cesari. 1998. "HIV Prevention with Drug-Using Populations—Current Status and Future Prospects: Introduction and Overview." *Public Health Reports* 113 (Suppl. 1): 4–18.
- Newell, M. L. 2003. "Antenatal and Perinatal Strategies to Prevent Mother-to-Child Transmission of HIV Infection." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 97 (1): 22–24.
- Ngugi, E. N., F. A. Plummer, J. N. Simonsen, D. W. Cameron, M. Bosire, P. Waiyaki, and others. 1988. "Prevention of Transmission of Human Immunodeficiency Virus in Africa: Effectiveness of Condom Promotion and Health Education among Prostitutes." *Lancet* 2 (8616): 887–90.
- Nijhuis, M., S. Deeks, and C. Boucher. 2001. "Implications of Antiretroviral Resistance on Viral Fitness." *Current Opinions in Infectious Diseases* 14 (1): 23–28.
- Norr, K. F., J. L. Norr, B. J. McElmurry, S. Tlou, and M. R. Moeti. 2004. "Impact of Peer Group Education on HIV Prevention among Women in Botswana." *Health Care for Women International* 25 (3): 210–26.
- Orroth, K. K., E. L. Korenromp, R. G. White, A. Gavyole, R. H. Gray, and L. Muhangi. 2003. "Higher-Risk Behaviour and Rates of Sexually Transmitted Diseases in Mwanza Compared to Uganda May Help Explain HIV Prevention Trial Outcomes." *AIDS* 17 (18): 2653–60.
- Over, M., P. Heywood, J. Gold, I. Gupta, S. K. Hira, and E. Marseille. 2004. *HIV/AIDS Treatment and Prevention in India: Modeling the Cost and Consequences*. Health, Nutrition, and Population Series. Washington, DC: World Bank.
- Over, M., and P. Piot. 1996. "Human Immunodeficiency Virus Infection and Other Sexually Transmitted Diseases in Developing Countries: Public Health Importance and Priorities for Resource Allocation." *Journal of Infectious Diseases* 174 (Suppl. 2): S162–75.
- Oyugi, J., and D. Bangsberg. 2004. "Treatment outcomes and adherence to generic Triomune® and Maxivir® therapy in Kampala, Uganda." XV International AIDS Conference. Bangkok, Thailand, July 10–16.
- Palella, F. J., K. M. Delaney, A. C. Moorman, M. O. Loveless, J. Fuhrer, G. A. Satten, and others. 1998. "Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection." HIV Outpatient Study Investigators. *New England Journal of Medicine* 338 (13): 853–60.
- Palella, F. J., M. Deloria-Knoll, J. S. Chmiel, A. C. Moorman, K. C. Wood, A. E. Greenberg, and others. 2003. "Survival Benefit of Initiating Antiretroviral Therapy in HIV-Infected Persons in Different CD4+ Cell Strata." *Annals of Internal Medicine* 138 (8): 620–26.
- Pape, J. W., S. S. Jean, J. L. Ho, A. Hafner, and W. D. Johnson. 1993. "Effect of Isoniazid Prophylaxis on Incidence of Active Tuberculosis and Progression of HIV Infection." *Lancet* 342 (8866): 268–72.
- Pauw, J., J. Ferrie, R. Rivera-Villegas, J. Medrano-Martinez, A. Gorter, and M. Egger. 1996. "A Controlled HIV/AIDS-Related Health Education Programme in Managua, Nicaragua." *AIDS* 10 (5): 537–44.
- Peak, A., S. Rana, S. H. Maharjan, D. Jolley, and N. Crofts. 1995. "Declining Risk for HIV among Injecting Drug Users in Kathmandu, Nepal: The Impact of a Harm-Reduction Programme." *AIDS* 9 (9): 1067–70.
- Peersman, G., and J. Levy. 1998. "Focus and Effectiveness of HIV-Prevention Efforts for Young People." *AIDS* 12 (Suppl. A): S191–96.
- Peipert, L., and Coffey, S. "About the Antiretroviral Drug Profiles." In HIV InSite Knowledge Base, ed. L. Peipert, S. Coffey, P. Volberding. <http://hivinsite.ucsf.edu>.
- Peterman, T. A., R. L. Stoneburner, J. R. Allen, H. W. Jaffe, and J. W. Curran. 1988. "Risk of Human Immunodeficiency Virus Transmission from Heterosexual Adults with Transfusion-Associated Infections." *Journal of the American Medical Association* 259 (1): 55–58.
- PETRA Study Team. 2002. "Efficacy of Three Short-Course Regimens of Zidovudine and Lamivudine in Preventing Early and Late Transmission of HIV-1 from Mother to Child in Tanzania, South Africa, and Uganda: A Randomised, Double-Blind, Placebo-Controlled Trial." *Lancet* 359 (9313): 1178–86.
- Pinkerton, S. D., D. R. Holtgrave, and F. R. Bloom. 1998. "Cost-Effectiveness of Post-Exposure Prophylaxis Following Sexual Exposure to HIV." *AIDS* 12 (9): 1067–78.
- Pinkerton, S. D., D. R. Holtgrave, W. J. DiFranceisco, L. Y. Stevenson, and J. A. Kelly. 1998. "Cost-Effectiveness of a Community-Level HIV Risk Reduction Intervention." *American Journal of Public Health* 88 (8): 1239–42.
- Pistone, T., S. Kony, M. A. Faye-Niang, C. T. Ndour, P. M. Gueye, D. Henzel, and others. 2002. "A Simple Clinical and Paraclinical Score Predictive of CD4 Cell Counts below 400/mm<sup>3</sup> in HIV-Infected Adults in Dakar University Hospital, Senegal." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 96 (2): 167–72.
- Quinn, T. C., M. J. Wawer, N. Sewankambo, D. Serwadda, C. Li, F. Wabwire-Mangen, and others. 2000. "Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1" Rakai Project Study Group. *New England Journal of Medicine* 342 (13): 921–29.
- Ramsay, S. 2003. "Leading the Way in African Home-Based Palliative Care." *Lancet* 362 (9398): 1812–13.
- Read, J. S. 2003. "Human Milk, Breastfeeding, and Transmission of Human Immunodeficiency Virus Type 1 in the United States." American Academy of Pediatrics Committee on Pediatric AIDS. *Pediatrics* 112 (5): 1196–205.
- Rely, K., S. Bertozzi, C. Avila-Figueroa, and M. T. Guijarro. 2003. "Cost-Effectiveness of Strategies to Reduce Mother-to-Child HIV Transmission in Mexico, a Low-Prevalence Setting." *Health Policy and Planning* 18 (3): 290–98.
- Reynolds, H. W., B. Janowitz, R. Homan, and L. Johnson. 2004. "Cost-Effectiveness of Two Interventions to Avert HIV-Positive Births." Poster presentation at the XV International AIDS Conference, Bangkok, Thailand, July 11–16, 2004.
- Reynolds, S. J., M. E. Shepherd, A. R. Risbud, R. R. Gangakhedkar, R. S. Brookmeyer, A. D. Divekar, and others. 2004. "Male Circumcision and Risk of HIV-1 and Other Sexually Transmitted Infections in India." *Lancet* 363 (9414): 1039–40.
- Royce, R. A., A. Sena, W. Cates, and M. S. Cohen. 1997. "Sexual Transmission of HIV." *New England Journal of Medicine* 336 (15): 1072–78.
- Saavedra, J. 2000. "Economy and AIDS in Latin America." In *AIDS in Latin America: A Multidisciplinary Vision*, ed. by J. A. Izazola. Mexico City: FUNSALUD.
- Salomon, H., M. A. Wainberg, B. Brenner, Y. Quan, D. Rouleau, P. Cote, and others. 2000. "Prevalence of HIV-1 Resistant to Antiretroviral Drugs in 81 Individuals Newly Infected by Sexual Contact or Injecting Drug Use." Investigators of the Quebec Primary Infection Study. *AIDS* 14 (2): F17–23.
- Saunderson, P. R. 1995. "An Economic Evaluation of Alternative Programme Designs for Tuberculosis Control in Rural Uganda." *Social Science and Medicine* 40 (9): 1203–12.
- Schneider, M. M., T. L. Nielsen, S. Nelsing, A. I. Hoepelman, J. K. Eeftink Schattenkerk, Y. van der Graaf, and others. 1995. "Efficacy and Toxicity of Two Doses of Trimethoprim-Sulfamethoxazole as Primary Prophylaxis against *Pneumocystis carinii* Pneumonia in Patients with Human Immunodeficiency Virus: Dutch AIDS Treatment Group." *Journal of Infectious Diseases* 171 (6): 1632–36.
- Selik, R. M., E. T. Starcher, and J. W. Curran. 1987. "Opportunistic Diseases Reported in AIDS Patients: Frequencies, Associations, and Trends." *AIDS* 1 (3): 175–82.
- Semba, R. D., N. Kumwenda, D. R. Hoover, T. E. Taha, T. C. Quinn, L. Mtimavalye, and others. 1999. "Human Immunodeficiency Virus

- Load in Breast Milk, Mastitis, and Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1." *Journal of Infectious Diseases* 180 (1): 93–98.
- Sengupta, D., S. Lal, and Srinivas. 1994. "Opportunistic Infection in AIDS." *Journal of the Indian Medical Association* 92 (1): 24–26.
- Shaffer, N., R. Chuachoowong, P. A. Mock, C. Bhadrakom, W. Siriwasin, N. L. Young, and others. 1999. "Short-Course Zidovudine for Perinatal HIV-1 Transmission in Bangkok, Thailand: A Randomised Controlled Trial." Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 353 (9155): 773–80.
- Shelburne, S. A., F. Visnegarwala, J. Darcourt, E. A. Graviss, T. P. Giordano, A. C. White Jr., and others. 2005. "Incidence and Risk Factors for Immune Reconstitution Inflammatory Syndrome during Highly Active Antiretroviral Therapy." *AIDS* 19 (4): 399–406.
- Sikkema, K. J., J. A. Kelly, R. A. Winett, L. J. Solomon, V. A. Cargill, R. A. Roffman, and others. 2000. "Outcomes of a Randomized Community-Level HIV Prevention Intervention for Women Living in 18 Low-Income Housing Developments." *American Journal of Public Health* 90 (1): 57–63.
- Spector, S. A., G. F. McKinley, J. P. Lalezari, T. Samo, R. Andruczk, S. Follansbee, and others. 1996. "Oral Ganciclovir for the Prevention of Cytomegalovirus Disease in Persons with AIDS: Roche Cooperative Oral Ganciclovir Study Group." *New England Journal of Medicine* 334 (23): 1491–97.
- Stanton, B. F., X. Li, J. Kahihuata, A. M. Fitzgerald, S. Neumbo, G. Kanduuombe, and others. 1998. "Increased Protected Sex and Abstinence among Namibian Youth Following a HIV Risk-Reduction Intervention: A Randomized, Longitudinal Study." *AIDS* 12 (18): 2473–80.
- Stanton, B. F., X. Li, I. Ricardo, J. Galbraith, S. Feigelman, and L. Kaljee. 1996. "A Randomized, Controlled Effectiveness Trial of an AIDS Prevention Program for Low-Income African-American Youths." *Archives of Pediatric Adolescent Medicine* 150 (4): 363–72.
- Stolte, I. G., N. H. Dukers, J. B. de Wit, J. S. Fennema, and R. A. Coutinho. 2001. "Increase in Sexually Transmitted Infections among Homosexual Men in Amsterdam in Relation to HAART." *Sexually Transmitted Infections* 77 (3): 184–86.
- Stover, J., N. Fuchs, D. Halperin, A. Gibbons, and D. Gillespie. 2003. "Costs and Benefits of Adding Family Planning to Services to Prevent Mother-to-Child Transmission of HIV (PMTCT)." Unpublished paper. The Futures Group.
- Stover, J., N. Walker, G. P. Garnett, J. A. Salomon, K. A. Stanekci, P. D. Ghys, and others. 2002. "Can We Reverse the HIV/AIDS Pandemic with an Expanded Response?" *Lancet* 360 (9326): 73–77.
- Stringer, E. M., M. Sinkala, J. S. Stringer, E. Mzyece, I. Makuka, R. L. Goldenberg, and others. 2003. "Prevention of Mother-to-Child Transmission of HIV in Africa: Successes and Challenges in Scaling Up a Nevirapine-Based Program in Lusaka, Zambia." *AIDS* 17 (9): 1377–82.
- Sweat, M. D., S. Gregorich, G. Sangiwa, C. Furlonge, D. Balmer, C. Kamenga, and others. 2000. "Cost-Effectiveness of Voluntary HIV-1 Counseling and Testing in Reducing Sexual Transmission of HIV-1 in Kenya and Tanzania." *Lancet* 356 (9224): 113–21.
- Sweat, M. D., K. R. O'Reilly, G. P. Schmid, J. Denison, and I. de Zoysa. 2004. "Cost-Effectiveness of Nevirapine to Prevent Mother-to-Child HIV Transmission in Eight African Countries." *AIDS* 18 (12): 1661–71.
- Tsunekawa, K., S. Moolphate, H. Yanai, N. Yamada, S. Summanapan, and J. Ngamvithayapong. 2004. "Care for People Living with HIV/AIDS: An Assessment of Day Care Centers in Northern Thailand." *AIDS Patient Care and Sexually Transmitted Diseases* 18 (5): 305–14.
- UNAIDS (Joint United Nations Programme on HIV/AIDS). 1997. *Blood Safety and AIDS: UNAIDS Point of View*. Geneva: UNAIDS.
- . 2000. *AIDS: Palliative Care*. UNAIDS Technical Update. Geneva: UNAIDS.
- . 2001. *Eight Case Studies of Home and Community Care for and by People with HIV/AIDS*. Geneva: UNAIDS.
- . 2004. *AIDS Epidemic Update: December 2004*. Geneva: UNAIDS.
- . 2005. *AIDS Epidemic Update*. December 2005. Geneva: UNAIDS.
- UNDP (United Nations Development Programme). 2004. *Thailand's Response to HIV/AIDS: Progress and Challenges*. Bangkok: UNDP.
- UNICEF (United Nations Children's Fund), UNAIDS (Joint United Nations Programme on HIV/AIDS), WHO (World Health Organization), and Médecins sans Frontières. 2004. *Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS*. Geneva: WHO.
- USAID (United States Agency for International Development). 2002. *What Happened in Uganda?* Washington, DC: USAID.
- Uys, L., and M. Hensher. 2002. "The Cost of Home-Based Terminal Care for People with AIDS in South Africa." *South African Medical Journal* 92 (8): 624–28.
- Van Liere, M. 2002. "HIV/AIDS and Food Security in Sub-Saharan Africa." Paper presented at the Seventh Annual Economic Community of West African States Nutrition Forum. Banjul, The Gambia, September 2–6.
- Vanek, J., O. Jirovec, and J. Lukes. 1953. "Interstitial Plasma Cell Pneumonia in Infants." *Annals of Paediatrics* 180: 1–21.
- Vickerman, P., F. Terris-Prestholt, S. Delany, L. Kumaranayake, H. Rees, and W. Watts. Forthcoming. "Are Targeted HIV Prevention Activities Still Cost-Effective in High Prevalence Settings? Results from an STI Treatment Intervention for Sex Workers in Hillbrow, South Africa." *Sexually Transmitted Diseases*.
- Vlahov, D., B. Junge, R. Brookmeyer, S. Cohn, E. Riley, H. Armenian, and others. 1997. "Reductions in High-Risk Drug Use Behaviors among Participants in the Baltimore Needle Exchange Program." *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 16 (5): 400–6.
- Vlahov, D., A. Munoz, J. C. Anthony, S. Cohn, D. D. Celentano, and K. E. Nelson. 1990. "Association of Drug Injection Patterns with Antibody to Human Immunodeficiency Virus Type 1 among Intravenous Drug Users in Baltimore, Maryland." *American Journal of Epidemiology* 132 (5): 847–56.
- Voluntary HIV-1 Counseling and Testing Efficacy Study Group. 2000. "Efficacy of Voluntary HIV-1 Counseling and Testing in Individuals and Couples in Kenya, Tanzania, and Trinidad: A Randomized Trial." *Lancet* 356: 103–12.
- Walker, D. 2003. "Cost and Cost-Effectiveness of HIV/AIDS Prevention Strategies in Developing Countries: Is There an Evidence Base?" *Health Policy and Planning* 18 (1): 4–17.
- Watts, C., H. Goodman, and L. Kumaranayake. 2000. "Improving the Efficiency and Impact of Blood Transfusion Services in the Context of Increasing HIV Prevalence." Health Policy Unit, London.
- Wawer, M. J., N. K. Sewankambo, D. Serwadda, T. C. Quinn, L. A. Paxton, N. Kiwanuka, and others. 1999. "Control of Sexually Transmitted Diseases for AIDS Prevention in Uganda: A Randomised Community Trial." Rakai Project Study Group. *Lancet* 353 (9152): 525–35.
- Wegner, S. A., S. K. Brodine, J. R. Mascola, S. A. Tasker, R. A. Shaffer, M. J. Starkey, and others. 2000. "Prevalence of Genotypic and Phenotypic Resistance to Anti-Retroviral Drugs in a Cohort of Therapy-Naive HIV-1 Infected U.S. Military Personnel." *AIDS* 14 (8): 1009–15.
- Weiss, H. A., M. A. Quigley, and R. J. Hayes. 2000. "Male Circumcision and Risk of HIV Infection in Sub-Saharan Africa: A Systematic Review and Meta-Analysis." *AIDS* 14 (15): 2361–70.

- Wenk, R., M. Bertolino, and J. Pussetto. 2000. "Direct Medical Costs of an Argentinean Domiciliary Palliative Care Model." *Journal of Pain and Symptom Management* 20 (3): 162–65.
- WHO (World Health Organization). 2002a. "Blood Safety: Aide-Memoire for National Blood Programmes." WHO, Geneva.
- . 2002b. "Definition of Palliative Care." WHO, Geneva.
- . 2004. "Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach." WHO, Geneva.
- WHO (World Health Organization) and UNAIDS (Joint United Nations Programme on HIV/AIDS). 2003. "Expert Group Stresses That Unsafe Sex Is Primary Mode of HIV Transmission in Africa." Press release, Geneva, March 14.
- Wiktor, S. Z., E. Ekpini, J. M. Karon, J. Nkengasong, C. Maurice, S. T. Severin, and others. 1999. "Short-Course Oral Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Abidjan, Côte d'Ivoire: A Randomised Trial." *Lancet* 353 (9155): 781–85.
- Wiley, J. A., S. J. Herschkorn, and N. S. Padian. 1989. "Heterogeneity in the Probability of HIV Transmission per Sexual Contact: The Case of Male-to-Female Transmission in Penile-Vaginal Intercourse." *Statistics in Medicine* 8 (1): 93–102.
- Wilkinson, D., K. Floyd, and C. F. Gilks. 1998. "Antiretroviral Drugs as a Public Health Intervention for Pregnant HIV-Infected Women in Rural South Africa: An Issue of Cost-Effectiveness and Capacity." *AIDS* 12 (13): 1675–82.
- Willbond, B., P. Thottingal, J. Kimani, L. M. E. Vaz, and F. A. Plummer. 2001. "The Evidence Base for Interventions in the Care and Management of AIDS in Low and Middle Income Countries." Commission on Macroeconomics and Health Working Paper Series, Paper WG5: 29. Commission on Macroeconomics and Health, Geneva.
- World Bank. 1997. *Confronting AIDS: Public Priorities in a Global Epidemic*. New York: Oxford University Press.
- . 1999. "Project Appraisal Document on a Proposed Credit in the Amount of SDR 140.82 Million to India for Second National HIV/AIDS Control Project." World Bank, Washington, DC.
- World Food Programme. 2001. *Food Security and HIV/AIDS: WFP Executive Board Third Regular Session*. Rome: WFP.
- WTO (World Trade Organization). 2003. "Decision Removes Final Patent Obstacle to Cheap Drug Imports." Press release, August 30.
- Yeni, P. G., S. M. Hammer, M. S. Hirsch, M. S. Saag, M. Schechter, C. C. Carpenter, and others. 2004. "Treatment for Adult HIV Infection: 2004 Recommendations of the International AIDS Society–USA Panel." *Journal of the American Medical Association* 292 (2): 251–65.

