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
- 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.

Source: Authors.

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 autocorrection 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 autofeedback 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+	
Deaths				
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
Disability-adjusted life years				
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 (Auvert 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 (Auvert 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[a]	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
	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
Peer-based programs	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
	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[a]	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

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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[a]	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[b]	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.	Ayouba 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 theses 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'Diekhor 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

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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
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 (Kumaranayake 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	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	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 (Vickerman 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)	Zambia (E) US$848 per HIV infection US$34 per DALY (Stringer and others 2003) Chad (AZT) US$924 to US$4,044 per HIV infection US$37 to US$162 per DALY (Hutton, Wyss, and N'Diekhor 2003) Chad (breastfeeding advice) US$1,241 to US$4,382 per HIV infection US$50 to US$175 per DALY (Hutton, Wyss, and N'Diekhor 2003)	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

(Continues on the following page.)

Table 18.4 Continued

Intervention	Epidemic profile (2001 US$)				UNAIDS estimate of need for 2007	
	Low-level epidemic (Middle East and North Africa)	Concentrated epidemic (East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, South Asia)	Generalized low-level epidemic (Sub-Saharan Africa)	Generalized high-level epidemic (Sub-Saharan Africa)	2003 US$ 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 (Kumaranayake 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)		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 Kumaranayake 2000) Zambia (E) US$41 per HIV infection US$2 per DALY (Foster and Buve 1995) 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)	Zimbabwe (E) US$166 to US$1,010 per HIV infection US$8 to US$51 per DALY (McFarland and others 1995)	230	2

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	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	No CE studies found	1	<1
Vaccines	No CE studies found	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	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'Diekhor (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'Diekhor 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 needlestick 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[a] (percent)	Prevalence in the general population (percent)	WHO region
Low level	< 5	< 1	Middle East and North Africa
Concentrated[b]	> 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
- 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).

Source: Authors.

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
- 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.

Source: Authors.

- 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 antiretroviral 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).

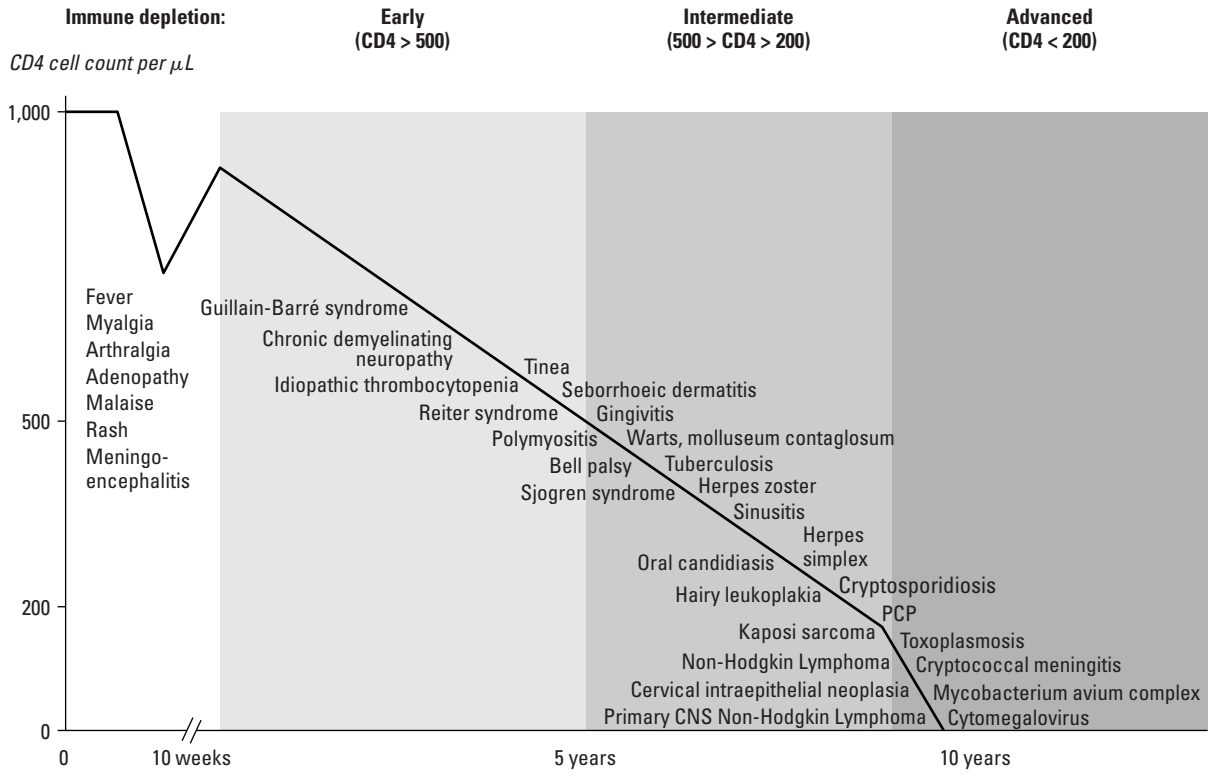
The World Food Program guidelines prioritize three nutrition interventions for people living with HIV/AIDS: counseling on specific behaviors, prescribed or targeted nutrition supplements, and links with food-based interventions and

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.



Source: Authors.

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*, *Aspergillis,* 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 oppportunistic 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 coinfected 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
HIV testing and diagnosis			
Confirmatory ELISA, Western blot	No cost-effectiveness studies found in developing countries	—	—
Palliative care			
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	—	—
Treatment of opportunistic infections, per episode			
Oral candidias	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 ambulatory: 2–16
		Short-course hospital: 3–8	Short-course hospital: 3–8
		Community-based directly observed therapy: 14–22	Community-based directly observed therapy: 14–22
Opportunistic infection prophylaxis			
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)
Early detection and screening for opportunistic infections			
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
Antiretroviral therapy			
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[a]	492/patient year[a]
	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 noninfectious (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 regimes, 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-naive 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.

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