
HIV/AIDS and Antiretroviral Therapy

This chapter presents some of the basic principles of HIV biology as a foundation for a discussion of the cost-effectiveness of treatment alternatives and of their intended and unintended consequences.

Natural History of HIV Infection without Antiretroviral Therapy

Epidemiologists use the term *natural history* to describe the sequence of symptoms and biological events that occur in the average untreated person suffering from a disease, from onset to recovery or death.

Biological Markers of HIV Disease

The natural history of HIV disease is one of a relentless battle between HIV and the immune system that results in progressive destruction of the body's capacity to fight serious infections and cancers. The period between infection and illness can be as short as a few weeks to as long as a few months, but in most cases, illness begins to seriously affect quality of life and economic potential within a median time of seven years. Once the characteristic opportunistic infections (OIs) or cancers emerge, which determine when the patient is classified as having AIDS, life expectancy declines sharply. Elements that influence the pace of disease progression include virulence of HIV; genetic, nutritional, and general health factors of the host; and access to therapies that ameliorate viral production (antiretroviral therapy) and mitigate the effects of OIs.

The most indicative biological marker of HIV disease progression is a decline in the number of CD4 cells (also known as *T4-helper cells*) in the blood. CD4 cells are critical to the body's immune response. When HIV enters the body, it binds itself to the CD4 cells, combines with the DNA in the cell nucleus, and eventually destroys the cells. At the initial infection stage, the level of circulating virus (viral load) is very high, and the CD4 count temporarily drops. However, soon after the initial infection stage, a balance is usually reached between the degree of viral replication and the immune control system that allows the CD4 count to recuperate. Over time, though, HIV progressively destroys the immune system until the CD4 count may drop to zero. As the CD4 cells become depleted, their function of protecting the body from a range of viral, fungal, and mycobacterial agents and tumors also declines to such low levels that those diseases cannot be controlled. At that stage, the body becomes highly susceptible to OIs and cancers (Gold and others 2005). An established relationship exists between the level of CD4 cells in the blood and the risk of development of OIs. In general, a CD4 count of less than 200 cells per cubic millimeter is regarded as the threshold for high risk for developing serious illnesses. As the CD4 count declines further, an increasing number of OIs begins to manifest, the most serious starting to appear when the CD4 count drops below 50 cells per cubic millimeter. A person's CD4 count is the best predictive marker of mortality associated with HIV disease. That count is also the best indicator of response to antiretroviral therapy (ART).

The Natural History of HIV in Thailand

Few fundamental differences can be identified between the natural history of HIV in Thailand and the history observed in most other middle-level or developed countries. In a large, prospective cohort study of HIV progression in Thailand, follow-up data on 757 HIV-infected patients indicated that progression rates are similar to those observed in cohorts in Australia, Europe, and the United States (Wannamethee and others 1998). However, other studies suggest that progression rates in Thailand may be more rapid than in Western cohorts. Table 3.1 presents a summary of those results. The data confirm that CD4 count is the most important single indicator of disease progression. For example, the table shows that 47.1 percent of the 169 HIV-infected patients with a first CD4 count of less than 200 cells per cubic millimeter devel-

oped AIDS within one year, as compared with 6.6 percent of those with an initial CD4 count of between 200 and 499 cells per cubic millimeter and as compared with 6.0 percent of those with a CD4 count above 500 cells per cubic millimeter. The table also shows that men progressed to AIDS somewhat faster than women and that increasing age was associated with HIV disease progression and mortality.

In a second natural history cohort study, 235 young Thai army recruits, whose seroconversion date was known, were followed for at least five years to determine progression to AIDS and death. Only two men in that cohort ever received ART, and in both cases, it was zidovudine (AZT) monotherapy. Also, only two men received treatment for latent tuberculosis (TB), and 12 men received trimethoprim-sulfamethoxazole prophylaxis for pneumocystis carinii pneumonia (PCP). Hence, that study may be as close to a natural history cohort as exists in Thailand. The mortality rate was found to be 56.3 deaths per 1,000 person years, nine times that of the HIV-negative controls. The five-year mortality rate of around 18 percent was twice as high as that of Western country cohorts. The median time to AIDS for those men, who were generally in the 15- to 24-year-old group, was 7.4 years, which is substantially less than that found in the analysis of natural history studies in Western countries.¹ The investigators also calculated the time from seroconversion to the first CD4 count of less than 200 cells per cubic millimeter, in order to estimate the time for optimal commencement of ART. That calculation revealed a period of 6.9 years, which was comparable to the time-to-AIDS calculation. The authors (Chin and others 2001) also calculated the 7-year AIDS-free rate of 57.0 percent, which indicates that HIV disease progressed relatively rapidly in that cohort compared with cohorts in Western countries.

In an attempt to explain those observations, the investigators (Chin and others 2001) note that the HIV viral load in their cohort at seroconversion was much higher than that found in other cohorts from Western countries. They also noted that the high viral load persisted for the first six months before settling to a level comparable to the Western cohorts after 12 months. They hypothesized that this very high viral load may influence the rate of disease progression and may, in some way, be related to infection with HIV subtype E, which is found in more than 95 percent of sexually transmitted HIV in Thailand. In another interesting observation to explain rapid progression rates, the investigators note the baseline CD4 count at seroconversion was a mean of 764

Table 3.1 Selected Characteristics and Disease Progression Rates in a Cohort of HIV-Infected Patients Managed at Chulalongkorn University Hospital, Thailand, 1998

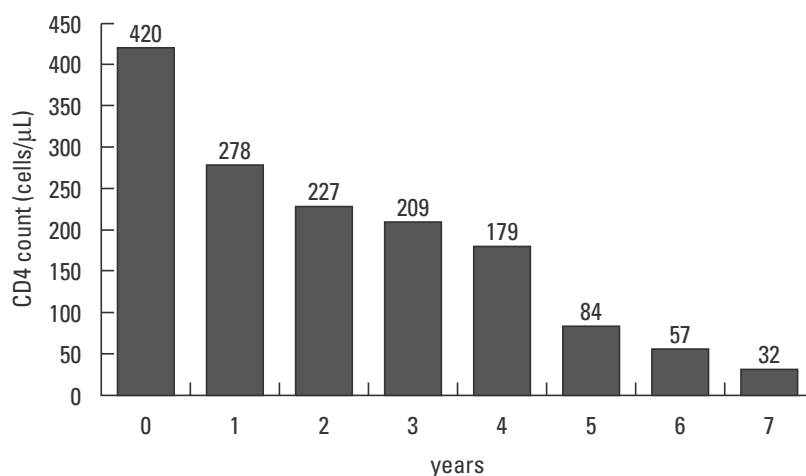
<i>Characteristic</i>	<i>Number of patients</i>	<i>Median CD4 count (cells/mm³)</i>	<i>Rate per 100 person years observed (%)</i>	<i>Relative risk (confidence interval) unadjusted/adjusted for initial CD4 count</i>
All	757	324	12.2	
<i>CD4 count (cells/mm³)</i>				
< 200	169	93	47.1	9.1 (5.4–16.0)
200–499	366	343	6.6	1.3 (0.7–2.3)
500+	222	713	6.0	1.0
<i>Risk group</i>				
Heterosexual	562	321	11.7	1.0
Homosexual	104	501	13.6	1.1 (0.7–1.9)/2.4 (1.4–4.0)
Injecting drug users	57	480	13.4	1.1 (0.5–2.4)/1.8 (0.9–3.9)
Other	19	588	6.9	0.6 (0.1–2.5)/1.8 (0.4–7.5)
<i>Sex</i>				
Male	644	355	13.1	1.0
Female	113	384	5.4	0.4 (0.2–0.9)/0.4 (0.2–1.0)
<i>Age at entry</i>				
< 20	23	471	0	1.0
20–29	343	373	10.8	1.4 (0.9–2.2)/1.1 (0.7–1.8)
30–39	233	324	13.7	1.6 (0.9–2.7)/1.3 (0.7–2.3)
40–49	115	332	14.5	
<i>Antiretrovirals (usually zidovudine)</i>				
No	452	456	9.2	1.0
Yes	305	277	15.5	1.7(1.2–2.5)/0.9(0.7–1.7)

Source: Adapted from Wannamethee and others 1998.

cells per cubic millimeter compared with a mean of 988 cells per cubic millimeter seen in the Multicenter AIDS Cohort Study in the United States (Enger and others 1996). That lower initial CD4 count in the Thai cohort may account for the early drop of CD4 to less than 200 cells per cubic millimeter, because the baseline is lower.

One of the most relevant markers of disease progression is the rate of CD4 cell destruction. A recent retrospective cohort study, which was conducted as part of the background research for this study at Siriraj University Hospital, suggests that the decline in CD4 counts among infected persons from Thailand mirrors observations in industrial countries of about 50 to 70 cells per year (Ratanasuwan 2004). That situation is illustrated in figure 3.1.

Figure 3.1 Decline in CD4 Count by Year of Follow-Up, Siriraj University Hospital, Thailand



Source: Ratanasuwan 2004.

Note: $n = 117$; mean follow-up is 48 months.

Transmission of HIV in Various Risk Groups

The main modes of transmission of HIV are well described and are documented both in a broad context and for Thailand in particular (MOPH and Division of Epidemiology various years; Phoolcharoen and others 2004b; World Bank 2000). A range of transmission risks by mode of transmission, drawn from worldwide experience (Royce and others 1997), is presented in table 3.2.

Table 3.2 Average Transmission Risk of HIV by Mode of Transmission

<i>Mode of transmission</i>	<i>Risk of infection</i>
<i>Sexual intercourse</i>	
Female-to-male transmission	1 in 700 to 1 in 3,000
Male-to-female transmission	1 in 200 to 1 in 2,000
Male-to-male transmission	1 in 10 to 1 in 1,600
Fellatio	1 in 13 to 1 in 17
<i>Needles</i>	
Needle stick	1 in 200
Needle sharing	1 in 150
Transfusion of infected blood	95 in 100
<i>Transmission from mother to infant</i>	
Without AZT treatment	1 in 3–5
With AZT treatment	< 1 in 10
Combination ART	1 in 50

Source: Adapted from Royce and others 1997.

Those are the average risks. However, for any particular individual, the specific risk of contracting HIV may vary significantly, depending on the combination of factors present at the time of exposure. The most critical aspects are the infectiousness of the infected person, which is positively correlated with his or her viral load, and the susceptibility of the person exposed, which is higher if the person has an ulcerative sexually transmitted infection (STI), is the receptive partner in sexual intercourse, or is an uncircumcised male. Different types of HIV may also have different capacities for infection. Subtype C, not prevalent in Thailand, is thought to be the most infectious.

Treatment of Opportunistic Infections with or without ART

Even as the availability of ART increases in many developing countries, appropriate diagnosis and management of life-threatening OIs and HIV-associated cancers still remain the most important aspects of the care of patients with HIV disease. OIs and cancers usually begin at least five to seven years after infection and occur progressively as uncontrolled HIV replication destroys the immune system (Colebunders and Latif 1991; Muñoz, Sabin, and Phillips 1997). When a person has an OI or cancer diagnosed clinically or by laboratory confirmation, he or she is regarded as having AIDS. The infections known as OIs are caused by organisms that exist in the environment of the body, such as on the skin, in the lungs, or in the gastrointestinal system; that remain latent until activated; and that become pathogenic when HIV has impaired the immunity system.

More than 20 different OIs and cancers have been associated with severe immune depletion. They include organisms from most biological categories of pathogens that can occur in our everyday environment. 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 reexposed to when immunosuppressed. In Western countries, the most common opportunistic diseases are cerebral toxoplasmosis, cryptococcal meningitis, cryptosporidium diarrhea, cytomegalovirus (CMV) retinitis, Kaposi's sarcoma, oesophageal candidiasis, and PCP (Bacellar and others 1994; Hoover and others 1993; Lanjewar and others 1996; Selik, Starcher, and Curran 1987). In Thailand and other resource-poor countries, because of the higher background incidence

Table 3.3 Prevalence of Selected OIs in Australia, India, Thailand, the United States, and Zaire, 1998.
percentage

<i>Opportunistic infection</i>	<i>Australia</i>	<i>India</i>	<i>Thailand</i>	<i>United States</i>	<i>Zaire</i>
Candidiasis	30	40–60	40	13	25
Cytomegalovirus	30	< 10	10	5	13
Cryptococcus	5–10	2–5	20	7	20
Pneumocystis carinii pneumonia	30–50	2–5	15–20	65	< 2%
Penicilliosis	Not seen	5	5–25	Not seen	Not seen
Toxoplasmosis	10	2	5	5	10
Tuberculosis	3	45–65	30–40	3	40

Source: UNAIDS 1998.

of other infectious agents, cryptococcal meningitis, infectious diarrhea, nonspecific wasting syndrome (slim disease), toxoplasma encephalopathy, and TB are more commonly encountered (see table 3.3) (Beji and others 1994; Chacko and others 1995; Hira, Dupont, Lanjewar, and others 1998; Hira, Dupont, and Sirisanthana 1998; Sengupta, Lal, and Shrinivas 1994; Unnikrishnan and others 1993).

The time from AIDS diagnosis to death depends on the type of OI, the availability of care, and the adherence of the patient to prescribed prophylaxis and treatment. Assigning a specific timeframe to survival from diagnosis of AIDS is becoming less relevant as accessibility to ART increases. Nevertheless, primary prophylaxis for OIs remains one of the most important ongoing and successful strategies in response to care of patients with progressive HIV disease. In Thailand, until relatively recently, the perception was that inadequate recognition of the role of prophylaxis was common; less than 50 percent of HIV-positive patients cared for by the Thai Network of People Living with AIDS, a nongovernmental organization (NGO) were covered by PCP prophylaxis (Wilson and Ford 2004; World Bank 2000). Community groups mounted a concerted campaign to increase awareness of the low costs and clear benefits of PCP prophylaxis, so that by 2002 health services increased its use to more than 85 percent (Wilson and Ford 2004).

In addition to differences in the background prevalence of certain infections, differences in the level of immunosuppression required before an AIDS-defining illness occurs also vary within countries and populations. TB, which causes significant mortality in the population

not infected by HIV, requires only moderate immune suppression before it can reactivate in previously exposed individuals. PCP usually occurs when CD4 cell counts have declined to below 200 cells per cubic millimeter, whereas CMV and atypical mycobacterial disease (mycobacterium avium complex, or MAC) usually arise when CD4 counts have dropped to below 50 cells per cubic millimeter (Selik, Starcher, and Curran 1987).

Starting ART in the presence of undiagnosed active TB may cause life-threatening complications because of immune reconstitution disease, which is expected to occur in up to 35 percent of patients who begin ART with a CD4 count of less than 50 cells per cubic millimeter. An important study from the Central Chest Hospital near Bangkok revealed disturbing information on HIV-TB coinfection (Punnotok and others 2000). In that study, conducted between 1995 and 1996, 2,587 newly registered patients with suspected pulmonary TB were considered for HIV screening. Of the 1,091 patients who had confirmed TB, the HIV prevalence was 22 percent. When those patients were compared with the HIV-negative TB patients, the authors found the HIV-TB patients were more likely to have isoniazid-resistant TB (10.9 percent compared with 3.5 percent) and multidrug-resistant TB (5.2 percent compared with 0.4 percent). That finding suggests that multidrug-resistant TB (MDR-TB) might develop among HIV-positive TB patients and then spread to HIV-negative people. Therefore, Thailand's policy of directly observed treatment of TB, which is designed to maximize adherence to TB treatment and to thus minimize the development of MDR-TB, is even more important for HIV-infected TB patients.

A common thought is that the differences in AIDS presentations in resource-poor countries, compared with Western countries, could be partially accounted for by few patients surviving their initial AIDS illnesses to become immunosuppressed enough to have reactivations of CMV or MAC. The widespread use of simple interventions, such as trimethoprim-sulfamethoxazole as PCP prophylaxis, has had a significant effect in delaying the onset of PCP, one of the most common initial AIDS-defining events, and has therefore positively influenced survival (Hoover and others 1993). However, prevention of PCP does not halt the relentless erosion of the immune system and prolongs life for only a short period. The only way to halt or delay progression of HIV disease is to interrupt viral replication, which is the aim of ART.

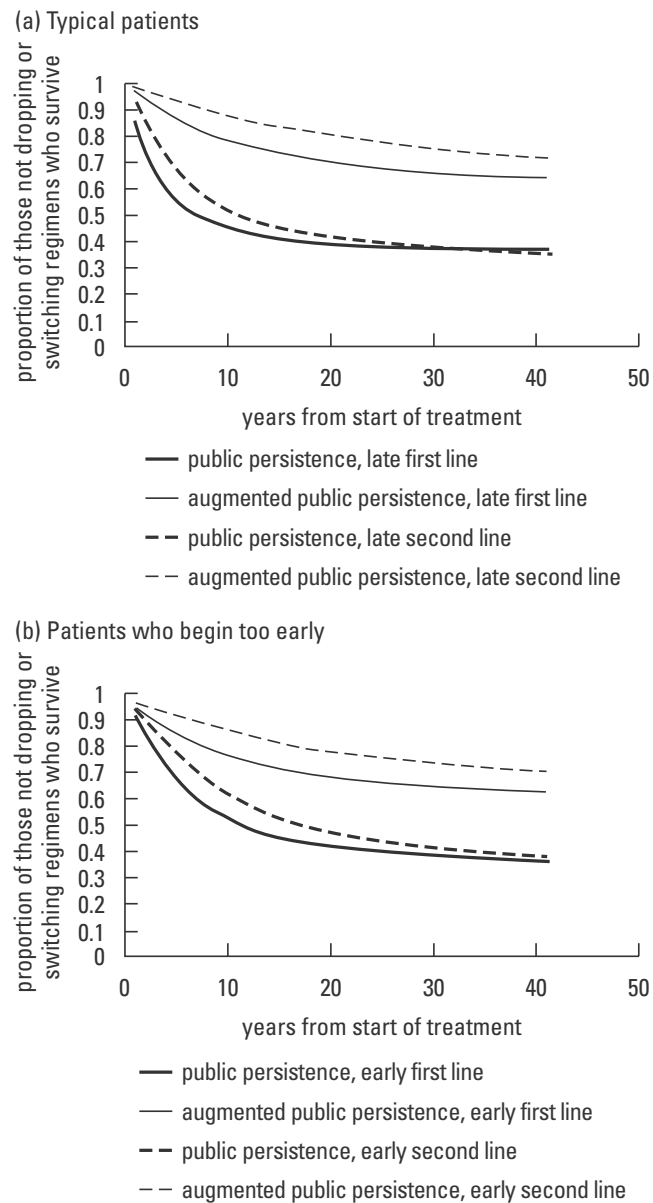
Effect of ART on Survival

The time path that an HIV-infected person follows from initial infection to the first symptoms of the disease and then to death and the response of that person to treatment are known to be highly variable and to depend on a host of characteristics of the individual, the virus, the treatment regimen, and the social context. Less well known, but equally crucial for projecting the result of the treatment policy are the effects of such variables on the propensity of individuals to seek ART and to persist with treatment once it has begun. Appendix A summarizes the empirical information available at the time of writing on the relationship between those variables and disease progression, as well as on the somewhat technically complex process by which we have estimated these patterns given the available information and expert opinion. This section synthesizes that discussion for a less technical audience.

To make projections under specific policy alternatives, we adopt a simplified set of assumptions about seeking of treatment, persistence with treatment, and survival as influenced by three of the many variables:

- whether treatment begins relatively early (at CD4 counts between 50 and 200 cells per cubic millimeter or relatively late (at a CD4 count of 50 cells per cubic millimeter or below)
- whether the provision of care is augmented by the presence of an effective group of people living with HIV and AIDS (PHAs)
- whether the patient is on first-line therapy or on second-line therapy.²

The two panels of figure 3.2 display our characterization of the literature and the opinions of our clinical experts regarding the cumulative proportion of patients who leave a treatment regimen either by dropping out or, for patients on first-line therapy, by moving from first-line to second-line therapy. Panel (a) gives the patterns for the typical patient, who begins treatment late. Panel (b) gives the pattern for patients who begin early. Two of the four patterns within each panel display the assumed dropout pattern for individual patients receiving public sector ART on first-line or second-line therapy. The horizontal axis measures the time from the beginning of that type of

Figure 3.2 Persistence Assumptions for Patients Receiving Public and Augmented Public ART

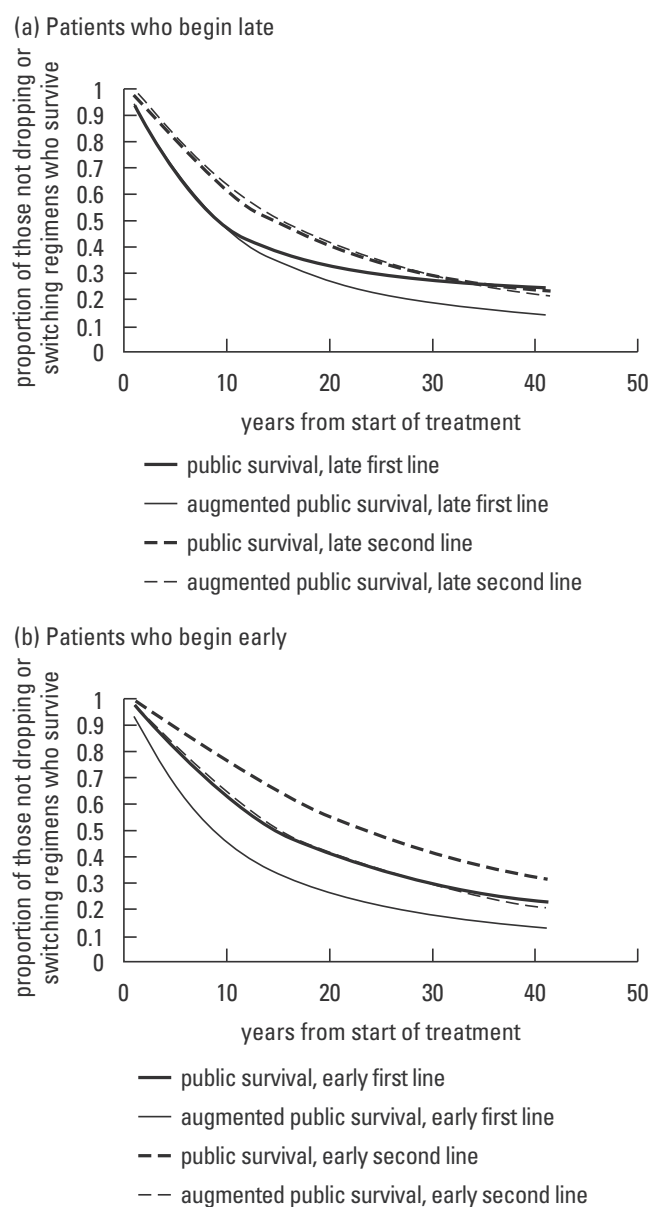
Source: Authors.

care. Because the typical patient on second-line therapy would be starting after several years of first-line therapy, the less successful survival is partly explained by these extra years of sickness.

A survival curve can then be defined that is conditional on patients not dropping out of treatment or, for those on first-line therapy, not moving on to second-line therapy. The two panels of figure 3.3 display our assumptions regarding the conditional survival of patients who do not drop out or move on to second-line therapy. Panel (a) gives the sur-

vival patterns for patients who begin late, when their CD4 counts are 50 cells per cubic millimeter or below. Panel (b) gives the survival patterns for early starters. The four patterns within each panel give the assumptions for the two public modes of treatment and for first-line and second-line therapies. As for figure 3.2, the less successful survival of those on second-line therapy is partly explained by the extra years of sickness already spent on ineffective first-line therapy. The patterns clearly show the greater presumed success of public therapy when it is augmented by a supportive PHA group that facilitates patient adherence.

Figure 3.3 Survival Assumptions for Patients Receiving Public and Augmented Public ART

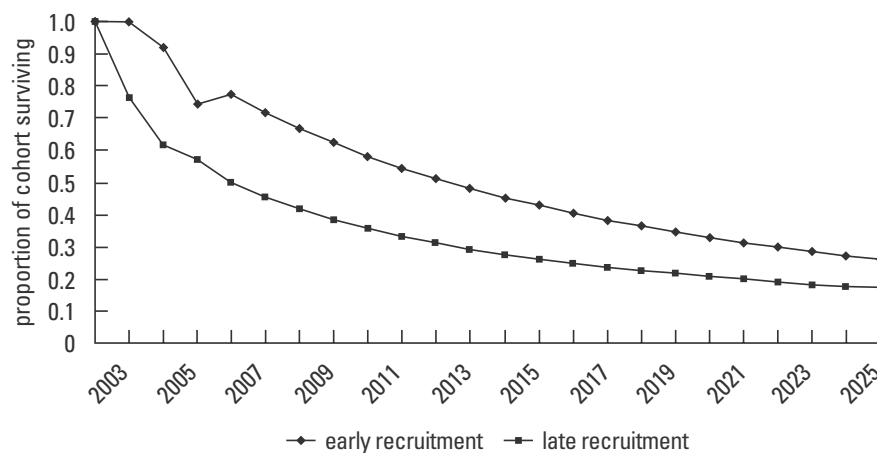


Source: Authors.

Patients who choose private sector care in Thailand are assumed to follow persistence and survival patterns identical to those that they would follow with augmented public care, hence obviating the need for the display of such patterns in the two figures. The report team believes that assumption is plausible because most private treatment in Thailand is of relatively high quality and because the patients who are willing and able to pay for private ART typically have the motivation and the social support to achieve high levels of adherence. Furthermore, in the face of growing competition from the augmented public system, private caregivers with low perceived success rates will fail to attract patients.

Because of the complexity of those options, direct computation does not easily yield an answer to this basic question: given the possibilities of dying, dropping out, or moving to second-line therapy, where the person might again drop out or die, what is the overall likely survival pattern of an individual who begins ART? The best way to derive such an answer is to use the Asian Epidemic Model (AEM) to assemble a pattern from all the possibilities. We do so by comparing the predictions of the AEM for our baseline—where there is very little ART—with the predictions from a specially constructed artificial scenario in which a single cohort of patients begins treatment in 2002, but new treatment starts revert to baseline levels in subsequent years. By comparing those two scenarios, we estimate the survival of the patients in that single 2002 cohort. Figure 3.4 presents the results.

Figure 3.4 Survival of a Model Cohort of Patients across First-Line and Second-Line Treatment Regimens If They Are Recruited Early or Late



Source: Authors.

As expected from the inputs to the model, the survival experience is markedly better for patients recruited early when their CD4 counts are between 50 and 200 cells per cubic millimeter than when they are recruited late, when their CD4 counts are 50 cells per cubic millimeter or below. By truncating the survival curve at 2025, the 23rd year, one can estimate the mean survival time for early and late recruits. The mean *additional* survival, starting at the time of treatment initiation and compared with no ART, of early recruits is 10.3 years compared with 8.0 years for those patients recruited at the lower CD4 count. Thus, for every new patient recruited into ART, those years of life accrue to the individual and to society as a whole in the year of recruitment.

To interpret those numbers, we recall that patients who are recruited early would be typically 18 to 30 months from death, whereas those recruited late would be between 6 and 12 months away. Thus, early recruitment to ART is estimated to add 10.3 years to the 18 to 30 months that the person would have survived, and late recruitment is estimated to add 8.0 years to the person's life expectancy. Therefore, according to this model and the assumptions detailed earlier, a person who begins treatment two years early adds more than those two years to his or her life expectancy. If we set aside for a moment the issue of discounting and all costs other than the person's time, the investment of the two years of treatment appears to be worthwhile from the individual's perspective: two years of early treatment yields three or four years of extra life.

When we estimate the cost-effectiveness of ART policies, we will use those incremental life-years saved per person who begins treatment as an incidence-based measure of benefit. Because those streams of 10.3 life-years or 8.0 life-years saved extend over time, they must be converted to discounted life-years using the discount rate used in the analysis. For example, if all costs and benefits are discounted at 3 percent, then the number of incremental life-years saved per new patient on ART become 7.9 and 6.5 discounted life-years saved, respectively.

Clinical Management of HIV Disease with ART

Management of ART is complex, and it requires not only significant capacity in terms of health service delivery, but also an accompanying range of counseling, testing, and laboratory services. Partly as a result of

those requirements, scaling up ART treatment presents serious practical challenges. Challenges exist in any setting and even more so in environments where essential physical and human infrastructure may be lacking. The risk of providing ART without strict adherence to guidelines and agreed standards of care is the propagation of multidrug-resistant HIV. Nevertheless, the success of pilot studies in Africa and Brazil suggest that ART can be adequately delivered in resource-constrained settings and that rates of adherence to ART in poor countries may be as high as, or higher than, rates in resource-rich countries. In Thailand, with the advent of the single-tablet GPO-vir, NGOs are reporting much higher rates of adherence than previously obtained under multiple-tablet mono and dual therapy. Médecins sans Frontières (MSF) reports adherence of greater than 95 percent in a cohort of more than 400 patients who have had the benefit of a structured community support network (Wilson and Ford 2004). Similarly, a recent rapid assessment of adherence among PHAs on ART in Chiang Mai in northern Thailand, carried out by the Thai Ministry of Public Health (MOPH) and the Population Council, shows adherence rates of about 85 percent (Community Medicine Department, Chiang Mai University 2002).³ Data from Siriraj University Hospital, however, suggest that good adherence cannot be automatically assumed: among 122 patients who started ART (with GPO-vir), only 60 percent were able to maintain an undetectable viral load after 12 months (Ratanasuwan 2004). The difference between the hospital's results and those obtained by MSF and in Chiang Mai may reflect the important role played by structured support networks and PHA peer groups in ensuring adherence. Interestingly, the Siriraj University Hospital adherence rate is similar to the rates expected in most cohorts in Western countries.

Diagnosis of HIV and Recruitment of Patients into ART

The ideal paradigm for care of people with HIV is by diagnosis of HIV in its early stages, preferably while they are well and before they have an opportunity to transmit HIV to their children or their sexual partners or through blood-to-blood contact. Diagnosis should be accompanied by counseling about their personal and public health responsibilities. Patients should then be monitored regularly until they develop an HIV-related illness or experience a drop in their CD4 count below 200 cells per cubic millimeter, and they should start ART

when they are adequately informed and have all necessary support systems to maximize adherence. Depending on the initial CD4 count, patients may need to be monitored only every six months. In Thailand, the current strategy of HIV diagnosis and recruitment of patients into ART is still working toward this ideal. Patients are generally diagnosed very late in their disease, when CD4 counts are well below 200 cells per cubic millimeter. The Thai Red Cross HIV/AIDS cohort, for example, reveals that 63 percent of attendees at the Anonymous Clinic between 1997 and 2003 had CD4 counts of less than 200 cells per cubic millimeter at the time of their HIV-positive diagnosis (table 3.4) (Duncombe 2004). Data from MOPH and MSF report similar findings. Late diagnosis and the ensuing need to start ART almost immediately could compound problems of poor adherence and could maximize the possibility of toxicity and of development of immune reconstitution disease.

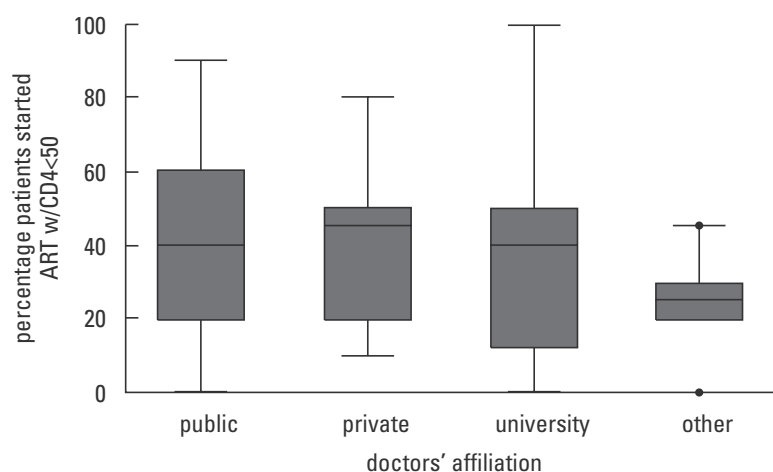
Additional data on the predominantly late diagnosis of HIV are available from the January 2004 and January 2005 surveys of Thai clinicians (Gold and others 2005). Doctors were asked to estimate the proportion of their patients who commenced ART at a CD4 count of less than 50 cells per cubic millimeter. Irrespective of their sector of affiliation (private, public, university, or other), Thai doctors reported having a large proportion of patients commencing ART at CD4 counts of below 50 cells per cubic millimeter (figure 3.5).

Other data suggest that as treatment becomes more available and as HIV is more widely accepted in Thai society, people are seeking testing in the earlier stages of their HIV disease. Data from the Thai Red Cross Anonymous Clinic show progressively earlier diagnosis from 1997 to 2003 (table 3.5). The data are encouraging in suggesting that availability of treatment could be used to strengthen voluntary counseling and testing efforts.

Table 3.4 Number of HIV-Positive Attendees at the Thai Red Cross Anonymous Clinic, Stratified by CD4 Cell Count, 1997–2003

<i>CD4 cell count (cells/mm³)</i>	<i>Number tested</i>	<i>Percentage of total</i>
< 100	6,655	41.3
100–200	3,554	22.0
200–350	3,133	19.4
> 350	2,784	17.3
Total	16,126	100.0

Source: Duncombe 2004.

Figure 3.5 Thai Doctors' Estimates of Patients Who Started ART with CD4 Counts of Less Than 50 Cells per cubic millimeter

Source: Gold, Duncombe, and Masaki 2005.

Table 3.5 Anonymous Clinic Attendees of Thai Red Cross Anonymous Clinic Whose CD4 Count Was Less Than 200 Cells per cubic millimeter, 1997–2003

Year	Number of CD4 cell counts performed	Attendees with CD4 < 200 cells/mm ³ (%)
1997	341	79.5
1998	1,387	84.4
1999	2,712	88.1
2000	2,706	52.8
2001	2,505	64.2
2002	3,194	55.9
2003 ^a	3,281	55.0
Overall	16,126	63.3

Source: Duncombe 2004.

a. Up to December 18.

To assess the importance of early diagnosis, one can compare the costs of care for patients who start ART while their immune function is still competent with the costs of care for those who start very late, as occurs throughout Thailand. Some indication may be gained from a recent Canadian study (Krentz, Auld, and Gill 2004). In that study, the authors compared a range of hospital and treatment costs for patients who presented for care at a CD4 count of less than 200 cells per cubic millimeter with costs for those patients who presented with a CD4 count of greater than 200 cells per cubic millimeter. Patients who presented with a CD4 count of less than 100 cells per cubic millimeter incurred almost three times the additional costs compared with those patients with CD4 counts greater than 200 cells per cubic

millimeter. Such costs were mainly attributed to hospitalizations and treatment for OIs before starting ART. This finding is confirmed for Thailand by a recent study that found that patients with CD4 counts of less than 50 cells per cubic millimeter at their first outpatient visit incurred costs on average 30 percent higher than those with CD4 counts of more than 200 cells per cubic millimeter (B 37,190 per year compared with B 28,986 per year) (Supakakunti and others 2004).

Clinical Challenges at Initiation of ART

Like all medications, ART has a range of potential toxicities that can vary from mildly irritating to life threatening. Although individual and class-specific toxicities are known, difficulties arise in trying to predict exactly which patient will develop toxicities and when and how that patient will respond to treatment of those adverse reactions. Drug toxicities compromise the benefits of ART, both in inducing potentially serious health problems and in reducing the chances of a patient remaining on therapy. Those effects can be considered either acute or chronic events. One must recognize that because of the differences in toxicities that may manifest within an individual, one drug from a particular class may be inappropriate, yet another drug from the same class may be well tolerated (Duncombe 2004; Gold and others 2005).

Concerns about the long-term development of drug toxicities have prompted medical authorities in many countries, including Thailand, to adopt a conservative approach to ART. Recent guidelines recommend ART for only those individuals in whom the risk of disease progression is greater than the possible drug-related concerns (Carpenter and others 2000). The following information on when and how to start ART is based on the National Guidelines for the Clinical Management of HIV Infection in Children and Adults (MOPH 2002).

When to Start?

The enrollment criteria for adults are as follows:

- AIDS
- Symptomatic HIV disease with or without a CD4 count of less than 250 cells per cubic millimeter (CDC clinical B or C)
- Asymptomatic HIV with CD4 count of less than 200 cells per cubic millimeter.

For children, the following enrollment criteria apply:

- All children less than 12 years old
- Children age 12 years or older with World Health Organization (WHO) clinical stage B and C or a CD4 count of less than 200 cells per cubic millimeter.

How to Start?

The recommended first-line antiretroviral regimen in Thailand is the fixed-dose combination of lamivudine, stavudine, and nevirapine, produced and sold by the Government Pharmaceutical Office (GPO) as GPO-vir.⁴ In addition, the MOPH has defined two alternative regimens for those patients who develop intolerance to one of the GPO-vir components. The three available first-line regimens under the National Access to Antiretroviral Program for People Living with HIV and AIDS (NAPHA) are as follows:

- stavudine + lamivudine + nevirapine (GPO-vir)
- stavudine + lamivudine + efavirenz
- stavudine + lamivudine + indinavir/ritonavir.

Some 80 percent of patients are estimated to be taking the first regimen, while an estimated 15 percent are taking the second regimen and an estimated 5 percent will eventually have to be moved to the third regimen.

The efficacy, safety, and tolerability of the GPO-vir combination in patients who are taking ART for the first time were recently evaluated by the multicountry 2NN study (van Leth and others 2004).⁵ The 2NN study was a randomized comparative open-label trial of first-line ART with regimens containing nevirapine, efavirenz, or both drugs combined in addition to stavudine and lamivudine in a treatment-naïve population. The characteristics of the population of patients in the 2NN study are similar to the population requiring ART in Thailand. The study enrolled 1,216 ART-naïve participants in 17 countries, with 200 enrolled at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) at the Thai Red Cross AIDS Research Centre in Bangkok. Among those participants, 607 were randomized to receive stavudine (40 milligrams twice daily if bodyweight is greater than 60 kilograms and 30 milligrams twice daily

Box 3.1 Key Challenges for Second-Line ART in Thailand

MOPH's second-line protocol is summarized as follows:

- failure based on drop of CD4 of more than 30 percent (immunological failure) or on occurrence of an OI after two years on ART (clinical failure)
- viral-load testing once per year (virological failure)
- resistance testing if viral load is greater than 5,000 copies per milliliter
- three alternative regimens:
 - didanosine+ lamivudine + idinavir/ritonavir
 - didanosine + lamivudine + lopinavir/ritonavir
 - lopinavir/ritonavir + saquinavir.

However, the existing protocol of second-line regimens in Thailand faces key challenges for successful implementation of ART because of late diagnosis of treatment failure, cross-resistance to many nucleoside reverse transcriptase inhibitor drugs, limited efficacy, and high costs of drugs. Thus, Thailand must investigate other policy options that lead to effective and sustainable implementation of the ART program.

Treatment Failure

Treatment failure can be detected in three ways:

- *Virological failure.* The patient's viral load becomes undetectable after ART begins, but later becomes detectable and generally increases over time. The cutoff of viral-load level that the doctor might use as a reason to change to a second-line regimen is not standard but depends on several factors, such as availability and cost of second-line drugs, the rate of rise of viral load, and the rate of decline of CD4 count.
- *Immunological failure.* This failure happens later than virological failure. After the level of HIV in the body has risen for some time, the CD4 count will fall. More than one definition of immunological failure exists: the WHO requires a fall of 50 percent and the MOPH requires a fall of 30 percent. Another problem is that the daily measurement of CD4 level is affected by many factors, such as concurrent infections.
- *Clinical failure.* Later still, after the CD4 count has fallen to low levels, the patient will develop an OI and become sick.

Thus, depending on how failure is diagnosed and how the criteria is used to make the diagnosis, failure may be early or late.

Resistance

At the start of the process of failure, HIV will probably be resistant to only one of the ARV drugs in the first-line regimen. Later, resistance may occur to the other drugs. In late failure, HIV will often be cross-resistant to other drugs of the same class that the patient has never taken. However, cross-resistance does not occur across different classes of drugs, only within each class. Many kinds of resistance exist, and in each class of drug, cross-resistance occurs at different rates and levels.

Box 3.1 Continued***Monitoring and Testing***

Compared with the past, enhanced possibility now exists to diagnose failure of first-line treatment. Such diagnosis is possible because of the increased availability and capacity of testing and monitoring of ART treatment, particularly through

- wider availability and lower cost of viral-load tests
- wider availability of HIV-resistance testing.

MOPH has introduced viral-load testing and a limited range of second-line anti-retroviral drug regimens into the national treatment program.

Cost of Second-Line ART

The cost of a second-line treatment program remains extremely high and also depends on many factors:

- price of testing (reagents and other costs) for viral load and resistance
- early or late diagnosis of failure, thus allowing a determination of which second-line drugs are likely to be effective
- number of patients whose failure was diagnosed clinically, immunologically, or virologically
- cutoff of viral load used for diagnosing failure
- price of the second-line drugs and availability of generic drugs or low-cost branded drugs.

if bodyweight is less than 60 kilograms), lamivudine (150 milligrams twice daily), and nevirapine (200 milligrams twice daily). Of the 607 participants randomized to this group, 387 were available for the first 48-week analysis. That analysis showed that 65.4 percent of those participating had a viral load of less than 50 copies per milliliter after one year of treatment with stavudine, lamivudine, and nevirapine. A moderate or severe rash associated with nevirapine was reported in 3.6 percent of the participants. Moderate or severe liver toxicity was reported in 7.8 percent of the participants. In the first 48 weeks of therapy, 22 percent of the participants changed ART.

Immune Reconstitution Syndrome

One of the challenges posed by late diagnosis of HIV and late commencement of ART is the increased risk of immune reconstitution syndrome (IRS). Restoration of immune function with ART can have

adverse consequences that may be confused with toxicity related directly to ART. IRS is caused by augmented immune responses to pathogens that are already present, but the mechanism is poorly understood. The incidence of IRS can be as high as 30 to 40 percent and is related to the degree of immune depletion present at the time of commencing ART. The most common IRS reactions are to cryptococcal infections and TB, and most occur within the first month of starting ART. IRS can also occur with most other OIs, including CMV, where patients may develop an immune recovery vitritis as many as eight months after commencing ART. The MSF experience with patients who begin ART when their CD4 count is greater than 50 cells per cubic millimeter is that up to 17 percent may die of AIDS-related complications, including IRS, within the first several months.⁶ In some centers, like Siriraj University Hospital in Bangkok, the approach to preventing IRS is to screen patients for OIs before they start ART. That screening process is appealing, but it can be expensive and is only practical only in major teaching hospital facilities. The most feasible option for ameliorating the effect of IRS is to encourage people to engage voluntary counseling and testing (VCT) services earlier in their illness and to begin ART when their CD4 count is about 200 cells per cubic millimeter.

Adherence to and Maximizing of the Benefits of ART

Treatment adherence or compliance broadly means the extent to which the patient follows medical instructions in taking his or her medications. It means taking the correct dosage, taking it the correct way, and taking it every time. Adherence is more difficult to maintain when medications need to be taken according to a precise schedule on a long-term basis, as is the case for many chronic illnesses, including HIV/AIDS. Those HIV medications that need to be taken on a long-term basis include ARTs, prophylactic medications for prevention of OIs, and medications for treatment of OIs (particularly TB). Maintenance of almost perfect adherence to ART is probably the most important determinant of success or failure of treatment.

Incontrovertible data suggest that adherence is one of the strongest predictors of CD4 count response to ART and therefore the best parameter of success. Wood and others (2004) evaluated the response of 1,522 ART-naive patients who were stratified by CD4 count and by subsequent adherence. The investigators stratified patients according

Box 3.2 Pediatric HIV/AIDS in Thailand

In 1991, the first pediatric HIV case was identified in Thailand. As of the end of 2005, about 42,000 cumulative cases of children with HIV infection were reported. Thailand has received international recognition for its effort in preventing mother-to-child transmission of HIV. A recent evaluation found that of 573,600 women who gave birth, 92 to 98 percent received prenatal care and 93.3 percent were tested for HIV. Of the 6,646 women who were found to be HIV positive, more than 90 percent received prenatal care and, of those, 4,659 (70.1 percent) received ART before delivery to prevent HIV transmission. Of the 6,475 infants born to the HIV-positive mothers, 5,741 (88.7 percent) received prophylactic ART. The number of new cases of infants with HIV infection in 2002 was between 600 and 800, down from almost 5,000 in 1998. Despite this impressive response, an estimated 25,000 children currently are living with HIV/AIDS, and at least one-half of them require ART to ameliorate the onset of severe HIV disease. The treatment of children with ART, as part of the MOPH Access to Care (ATC) initiative, began in 1998 with 800 children and was expanded to 2,000 children in 2000. Currently, all eligible children should have access to ART in Thailand.

Many complex issues arise in treating HIV-infected children, not the least of which is that one or both of their parents may already have died of AIDS. An estimated 300,000 AIDS orphans live in Thailand, so both HIV-infected and non-HIV-infected children may be living with grandparents, other relatives, or friends. These caretakers may not have sufficient time to ensure appropriate adherence to ART and management of toxicities and intercurrent infections for the HIV-infected children while still arranging for the needs and supervision of all the children in their care. Moreover, the impact of HIV disease on children goes beyond the range of OIs usually described in adults. Clear evidence demonstrates that HIV-infected children have significantly higher rates of psychiatric illness, especially depression and behavioral disorders, compared with their peers. Those problems will also affect their ability to take and adhere to ART. In Thailand, the outcomes of children on ART are, in general, parallel to those of adults.

Because most HIV-infected children will be diagnosed soon after birth, therapy should commence at the most opportune time. However, considerable international debate exists as to the best time to start ART and as to the most appropriate regimen. Some early data also suggest that, with careful monitoring, it may be possible to reduce ART toxicities by structured treatment interruptions in children with no loss of ART efficacy. The prevalence of known metabolic and physical (fat redistribution) toxicities associated with ART is as high in children as in adults. Moreover, other problems not prevalent in adults, such as bone mineral density abnormalities, for example, osteopenia (53 percent) and the more serious osteoporosis (23 percent) were observed in a cohort of children on ART in Texas.

The Thai network of clinical research in pediatric HIV/AIDS includes HIV-NAT and centers at Chulalongkorn University Hospital, Khon Kaen University, and Queen Sirikit National Institute of Child Health. HIV-NAT currently has initiated six pediatric studies, and five more are planned. HIV-NAT commenced its first pediatric study (HIV-NAT 010) in November 2001. That was a pilot study was designed to evaluate when to

start ART in HIV-infected children. Children with mild or moderate symptoms and with a CD4 cell count between 15 and 24 percent (moderate immune suppression) were randomized to start ART (GPO-vir) immediately or to wait until their CD4 count fell below 15 percent. That study enrolled 43 children at HIV-NAT and at Khon Kaen University. A study involving 300 children was proposed for 2004. HIV-NAT also follows 60 children who are being treated with highly active antiretroviral therapy (HAART) based on nonnucleoside reverse transcriptase inhibitors (NNRTIs) through the ATC program. Those patients are mainly older children with low CD4 counts who previously had no access to ART because of financial difficulties. In each of the past six months, approximately four new cases have appeared.

A cross-sectional study of genotypic resistance in 100 children treated with nucleoside reverse transcriptase inhibitors (NRTIs) was undertaken at HIV-NAT and Queen Sirikit National Institute of Child Health. The preliminary results show that a majority of children harbor reverse transcriptase mutations. In Thailand, until recently, dual NRTI has been the main ART regimen used. The results of that study will help providers to plan for salvage therapy in those children. HIV-NAT has also initiated two pharmacokinetic studies to find the ideal dosing of the following protease inhibitors in children. One study examines lopinavir/ritonavir + saquinavir, and the other study examines nelfinavir. Those studies are important because the correct dosages in children are not known. The lopinavir/ritonavir + saquinavir combination is a potential salvage regimen for children with resistance to the most widely used HAART in Thailand, GPO-vir.

HIV-NAT understands the importance of addressing psychosocial issues in children and families affected by HIV. HIV-NAT works closely with the Wednesday Friends Club, a peer support group of the Thai Red Cross AIDS Research Centre, to counsel caregivers. At each clinic, representatives from the Wednesday Friends Club hold individual and group counseling sessions with caregivers while the children play and listen to stories. HIV-NAT is exploring two main issues:

- the factors that affect adherence to ART and
- the reasons behind caregivers' decisions not to disclose to children their HIV diagnosis.

An added benefit of HIV-NAT pediatric studies is the opportunity to identify HIV-infected parents who have not sought care. Almost all of those parents now receive ART if appropriate. Clinical care is provided through HIV-NAT's adult clinical trials and ATC programs. In 2004, HIV-NAT planned to launch five new pediatric studies:

- a pharmacokinetic study of an investigational ART
- a structured treatment-interruption study
- a prospective cohort of 300 children on NNRTI-based HAART with seven sites in Thailand
- a salvage therapy study for children failing dual NRTIs
- the full study (following HIV-NAT 010) of immediate versus deferred ART initiation.

Source: Gold and others 2004.

to their CD4 count on initiation of ART. The time to record a rise of at least 50 cells per cubic millimeter was used as an indicator of response to therapy. Response was determined during each of five 15-week periods after therapy began. Adherence was calculated as the amount of medication required for perfect adherence divided by the actual amount of medication dispensed to each patient during the first year of treatment. The investigators used a cutoff level of 75 percent adherence as the indicator of adequate or inadequate adherence. Irrespective of the ART drugs used, statistically significant improvements in CD4 counts were seen between adherent and nonadherent patient groups at all strata of baseline CD4 counts. The investigators also conducted a univariate analysis for predictors of CD4 count response and found that male gender, increasing age, adherence, injecting drug use, and baseline HIV RNA were all significantly associated with CD4 cell response. In a subsequent multivariate analysis that controlled for those factors, male gender, adherence, protease inhibitor use, and baseline HIV RNA were all associated with a response (table 3.6).

A particularly important finding for the Thai situation was the relationship between baseline CD4 count, adherence, and response rate. The investigators conducted a more detailed analysis in which they looked at patients who had adherence of greater than 95 percent compared with the 75 to 95 percent group. They found a significant difference in the response rate at 24 months for patients who were 95 percent adherent (72.8 percent responsive) compared with the second strata, where the response rate was only 50.7 percent. Those observations indicate that considerable attention must be directed at the adherence of patients who begin ART at late stages of HIV disease in order to achieve the maximum benefit of therapy. The observations further reinforce the notion that it is never too late to begin therapy

Table 3.6 CD4 Count and Interquartile Range at the Fifth 15-week Follow-up Compared with the Baseline

<i>Baseline CD4 count</i>	<i>CD4 count (Interquartile range)</i>		<i>p Value</i>
	<i>Adherent</i>	<i>Nonadherent</i>	
< 50	200 (130–290)	60 (10–30)	$p = 0.009$
50–199	300 (180–390)	125 (40–210)	$p < 0.001$
> 200	550 (410–720)	300 (250–505)	$p < 0.001$

Source: Adapted from Woods and others 2004. Interquartile ranges are from Duncombe and others 2004.

and that substantial gains in CD4 counts can be achieved with excellent adherence. In that study, 39 percent of the patients presented with a CD4 count of less than 200 cells per cubic millimeter. The conclusion is that any triple combination ART will achieve significant patient benefit, if the therapy is taken as directed. One should note that all care for patients in that study was provided free of any charge.

Despite the advent of a reduced pill burden compared with five years ago, as well as less frequent dosing, adherence in HIV patients in developed countries is far from optimal, with most studies indicating a long-term adherence rate of less than 60 percent in community-based studies, as compared with the controlled and supported situation found in clinical trials. No strong evidence exists to suggest that people in resource-poor countries will adhere less to ART than their counterparts in resource-rich countries. Factors that appear to positively affect adherence in resource-rich country settings include the frequency of outpatient visits, education, age, and lifestyle factors (no alcohol or recreational drug use) (Kleeberger and others 2004). No comparable statistical research to date examines what factors affect adherence in Thailand. However, some qualitative evidence drawn from interviews and focus groups with PHAs does exist (box 3.3). From the perspective of PHAs, the medical and emotional side effects of ART and the lack of support and sufficient information about ART are major factors decreasing adherence. Lack of reliability in drug supply is also mentioned, as are financial costs.

One must also understand what providers feel are the determinants of good adherence. Table 3.7 reports the factors that respondents to the HIV-NAT Survey of Thai Physicians regarded as important in adherence to ART.

Increasing the effectiveness of interventions to improve adherence may have far greater effect on the health of the population than any improvement in specific medical treatments. The WHO reports that studies consistently find significant cost savings and increases in the effectiveness of health interventions that are attributable to low-cost interventions for improving adherence.

Development of Resistance and Its Effect on the Use of ART

Resistance to ARTs is probably the greatest threat to the control of HIV. As each new therapy is released and tested in the community,

Box 3.3 Behavioral Aspects of Adherence to ART in Thailand Based on Results from Interviews and Focus Groups with PHAs

Aim

This study assessed qualitative information from PHAs on their experience of accessing ART through the MOPH system and on their experience in taking ART, with the aim of determining factors that affect adherence and quality of life. In addition, the study was designed to record individual stories about their experience with the health care system as related to care and treatment.

Methodology

Using an open format, interviews and focus group discussions were conducted by Dr. Seri Phongphit with PHAs from Bangkok, Khon Kaen, and Suratthani. Students and staff from Chiang Mai University, Khon Kaen University, and Rajabhat Institute assisted with recording the responses at workshops and meetings.

Results

Because information was qualitative and subjective, it is appropriate to present it in narrative form. The general impressions can be summarized as follows:

- *Factors that improve adherence.* PHAs have an overwhelming feeling that wider availability of ART has given them hope where previously there was none. They are now able to plan for the future and to take care of their families by continuing to work. Because PHAs can now live a more normal life, they feel less stigma and discrimination. They feel they are less of a burden on society and are more accepted by their communities. Because many PHAs have seen their friends and family members die of AIDS, they believe that ART is a key to their continuing survival. The presence of community support networks is vital in providing stability to and continuity in taking ART. Education of family members is also important because they need to understand the rigorous effort required to take ART. The availability of ART through the public hospital system is important because it reduces the cost of ART, even though PHAs may still have to pay for monitoring tests.
- *Factors that impede adherence.* PHAs believe that when they start ART, they are not given enough information by prescribing doctors and the public health

resistant strains are identified that can result in either partial or complete drug resistance, depending on the particular genomic mutation. In countries where ART has been available for more than a decade, most HIV present in the community has at least one resistant mutation. The major underlying causes for drug resistance, which leads to

system, in general, about the side effects of ART, especially the immediate problems of nausea, diarrhea, change in mood, and rash, as well as the long-term issues of facial wasting and weight gain. Those side effects will encourage people to stop ART because many believe that ART is a cure, rather than needing to be taken on an ongoing basis. PHAs have the impression that the health care system imposes many lifestyle restrictions on them in order to be eligible for subsidized ART. They are told to avoid drinking alcohol, smoking, having children, and disclosing their HIV status to anyone, which is clearly an individual perception and not seen as universal in Thailand. Because they are diagnosed with HIV so late in their illness, PHAs feel that they need to start ART immediately and that they have no time to prepare socially and mentally for the commitment to taking ART. The “30-Baht” scheme provides considerable benefits, but it is not portable. Therefore, PHAs cannot access ART at hospitals outside their area of residence. Hospitals are usually visited as a last resort when PHAs are already ill. Because most voluntary counseling and testing services are located within the public hospital facility, they are not used early in HIV infection.

Opinions of numerous patients and doctors regarding factors that affect adherence have been gathered from the HIV-NAT conference survey and are shown in table 3.6. When we compare these opinions, we note a number of commonalities:

- improved education and information for patients, their family members, and health care workers
- subsidized HIV testing and monitoring to encourage patients to be tested earlier in their disease and to reduce the cost burden of treatment with ART
- community information programs to lessen the fear of HIV and to reduce stigma and discrimination
- government support for community support groups that provide essential support to help patients remain on ART

This behavioral survey underlines the fact that GPO-vir is an effective, relatively low-cost and low-toxicity treatment for HIV/AIDS, compared with the more toxic and expensive alternatives. It is essential that the health care system, at all levels, work with patients and the community to keep as many people on this therapy for as long as possible.

Source: Phongphit 2004.

treatment failure, are poor adherence, poor absorption, inadequate potency of the regimen, and drug-to-drug interaction that results in lowered blood levels. Resistant mutations develop simply because of Darwinian selection: if the drug level in plasma or cells is not high enough to suppress viral replication, then mutant strains will survive,

Table 3.7 Clinician Opinions on Reasons for Poor Adherence to ART
percentage

<i>Reasons for poor adherence</i>	<i>Very important</i>	<i>Important</i>	<i>Not important</i>
Financial difficulties	78.1	18.3	3.7
Medical side effects	53.7	42.7	3.7
Lifestyle factors	47.6	42.7	9.8
Social difficulties	45.7	48.2	6.2
Psychological difficulties	37.8	52.4	9.8
Illness associated with HIV	34.2	61.0	4.9
Medication factors	34.2	58.5	7.3
Concerns about confidentiality	30.5	56.1	13.4
Beliefs about effectiveness of treatment	29.3	43.9	26.8
Misunderstanding about need to take long term	26.8	62.2	11.0
Patient uncertainty about ability to adhere	23.5	63.0	13.6
Beliefs about HIV	19.5	69.5	11.0
Drug use	19.2	50.0	30.8
Alcohol use	17.5	46.3	36.3
Cultural belief	14.6	56.1	29.3
Beliefs about Western medicine	11.1	51.9	37.0

Source: Gold, Duncombe, and Masaki, 2004 and 2005

Note: Because of rounding, percentages may not total to 100.0 percent.

which are then selected for their drug-resistant capacity. Two types of resistance are measured:

- genotype, which determines the genetic sequencing of the viral genome and describes whether specific mutations that have been observed to confer resistance are present
- phenotype, which determines the susceptibility of viral culture to different concentrations of a drug.

When those measurements are taken together, they can provide a valuable guide to the potential efficacy of different drug concentrations. Unfortunately, the technology required to perform those tests is expensive (up to US\$600 per test) (B 24,000) and requires sophisticated laboratory support that is impractical to achieve in most settings. Resistance testing is not required to manage HIV appropriately because it is well accepted that monotherapy with any of the ART drugs will result in rapid development of resistance, as will

adherence of less than about 95 percent, irrespective of the ART combinations chosen. Authorities have argued that anything less than triple therapy will be ineffective in managing patients on ART because development of resistance is inevitable. However, in a recent retrospective cohort study at Lampang Hospital in northern Thailand, patients who were treated with dual therapy had a clear advantage in survival over patients who were treated with monotherapy or patients who received no ART at all. The effect of ART on mortality was quantified by using a hazard ratio, after adjusting for sex, age group, year of registration, clinical status at first visit, and CD4 count group. The adjusted hazard ratio of monotherapy to no therapy was 0.65 and to dual therapy was 0.43. Those ratios suggest that even a suboptimum ART regimen can have substantial survival benefits.

Between the inexpensive CD4 tests and the expensive genetic sequencing tests lie the viral-load tests, which currently cost B3,000 to B5,000 (US\$75–125) per test in Thailand. Because treatment failure in a patient often reveals itself as an increase in viral load before the CD4 count declines or OIs appear, viral-load tests are a useful signal to the clinician that it is time to switch the patient to second-line therapy. By switching therapies as soon as viral load begins to climb, the patient may avoid cross-resistance problems and thus have more success on second-line therapy. Therefore, incorporating viral-load tests into the cost of first-line therapy is justified if second-line therapy is available, but not otherwise.⁷

Community- and NGO-Based Support to Enhance Adherence

The supportive role of community in HIV care is a fundamental aspect of the Thai response to the HIV/AIDS epidemic. Community-based organizations have been involved in providing home-based and palliative care since the early days of the epidemic. That role has now expanded to supporting patients on ART and providing their family members with the necessary knowledge to enhance the patients' adherence. Preliminary data suggest much higher rates of adherence to ART when adequate support networks are in place. NGOs and community-based organizations are the main vehicles for such support. Box 3.5 gives examples of NGO and community-involvement in support and care of PHAs in Thailand.

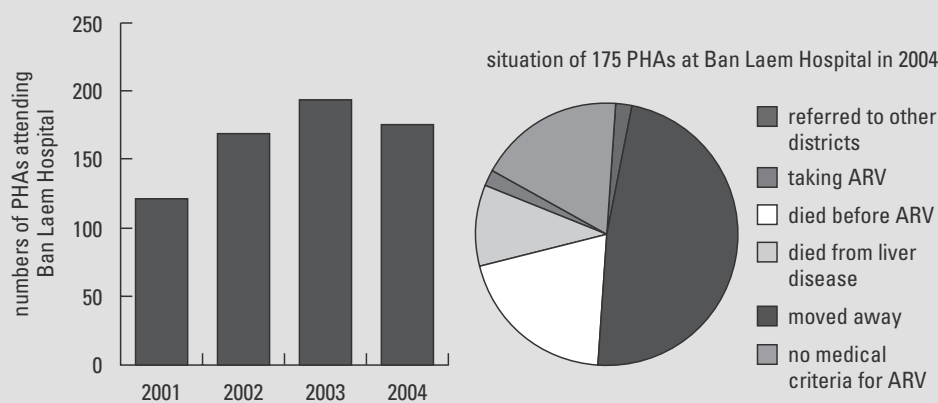
Box 3.4 Can Direct Observed Therapy Strategies Be Applied to Provide More Effective ART?

HIV management with ART is almost unique in medicine. It requires mostly young patients to take complex regimens over long periods with no respite and to maintain a minimum of 95 percent adherence. In the case of TB, for example, where similar regimens are taken for only some months, poor adherence led to a sweeping epidemic of multidrug-resistant TB (MDR-TB) that could only be prevented by introducing comprehensive directly observed treatment short course (DOTS) program. Although considering the use of DOTS for HIV is appealing, the long-term nature of treatment and the stigma attached to HIV disease are significant obstacles to this approach. Nevertheless, support is growing in international programs to use DOTS to expand ART. Evidence from small community-based treatment programs in Haiti, for example, suggest that DOTS with ART can be delivered effectively in poor settings if there is an uninterrupted supply of high-quality drugs (Farmer and others 2001a, 2001b).

In Thailand, this approach is gaining some currency, and with integration of the TB and HIV portfolios within MOPH, pilot studies will likely be used to test that strategy. The overlapping problems of HIV and TB are well known in Thailand, where TB represents about 40 percent of OIs. Following the rise of MDR-TB throughout Thailand, the MOPH strengthened the DOTS, which is now widespread and well accepted. The concept of using this process to provide lifelong therapy is appealing but not without problems. On the positive side, enabling TB and HIV therapy to be given simultaneously would allow the most efficient use of limited resources. Because HIV/TB coinfecting patients have a higher mortality rate than patients with TB alone, integration of therapy would reduce TB mortality rates. Integration of services may also reduce the stigma and discrimination felt by patients who are treated for HIV and TB separately and by different management strategies. However, a range of potentially negative consequences of integration also can occur. TB therapy usually consists of several drugs given twice a day, albeit with a limited time of treatment. The additional HIV drugs, with their own side effects and immune reconstitution problems, may have a negative impact on both programs. In addition, there are important drug interactions between HIV and TB therapies, although the WHO has introduced recommendations to adjust the dosage of efavirenz when used with rifampin-containing regimens. The incidence of immune reconstitution disease has been observed to be as high as 36 percent in patients with HIV/TB when they start on ART, which complicates early patient care because it may be impossible to distinguish this problem from the side effects of ART or the TB medication or from the appearance of new disease manifestations. In that regard, training and support of health care workers to provide appropriate standards of patient care is very challenging. Provision of HIV management through the TB DOTS network remains an appealing but unproven strategy to improve efficiency and enhance adherence. Thailand is in an ideal position to establish research projects to test this strategy in community-based settings where high levels of donor support are not used to affect outcomes.

Box 3.5 The Effect of a Comprehensive Care Program for PHA, Supported by MSF, in Ban Laem District Hospital

Ban Laem Hospital, 150 kilometers south of Bangkok in Petchburi province, is a 30 bed hospital serving a population of 45,000 people. In 2003, HIV prevalence in pregnant women in the region was 1.5 percent. In 1996, a senior nurse with a special interest in bereavement counseling set up a support group for relatives of patients who had died. As it happened, the three people who attended regularly were HIV-positive women whose husbands had died of AIDS. The group developed into a PHA peer support group; was named *Tan Tanod* (meaning palm sugar, a local product); and was formally launched in 1998 with a permanent meeting room in the hospital and with funding from the local government. At the request of the hospital, MSF provided training on health care and ongoing technical support for both hospital staff and PHAs. Tan Tanod currently has 114 members.



The antiretroviral (ARV) drug project in Ban Laem was launched in October 2001 with a 10-person project committee comprising four hospital staff members, four PHAs, and two MSF staff members. An HIV clinic was set up, initially on one day per week. In 2001, 120 PHAs visited the hospital for treatment. Soon after ARV drugs became available in the hospital, the number of PHAs visiting the hospital increased. The hospital has since moved from the concept of an ARV drug project with a limited quota of patients to the concept that AIDS is like other diseases, and all patients with clinical indications are treated with ARV drugs. Clinic days increased to twice weekly when the number of patients on ARV drugs increased beyond 75. Home visits are done three days per week—by PHAs on two days per week and jointly by PHAs and a nurse on the remaining day. In 2003, the hospital installed two condom vending machines; two condoms are dispensed for B 5 (US\$0.12).

During 2004, 175 PHAs visited the hospital for treatment. Among those PHAs, 4 came from other districts and were referred to their local hospital; 86 (49 percent) now take ARV drugs; 32 (18 percent) died before ARV drugs were initiated; and 13 (7 percent)—all with very low CD4 counts—died of OIs within two months of starting ARV drugs. One has since died of end-stage liver disease, and three others have moved to

Box 3.5 Continued

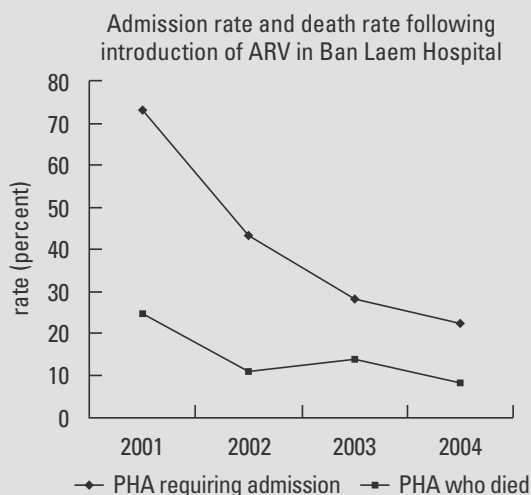
other districts. Thirty-six (21 percent) do not fulfill medical criteria to begin use of ARV drugs because they are asymptomatic and their CD4 count is above 250: all of these patients are women diagnosed as HIV positive during pregnancy or their male partners. Of the 120 PHAs who visited the hospital during 2001 before the ARV drug project began, 87 (79 percent) required admission and 30 (25 percent) died. By 2004, the admission rate had fallen to 22 percent, and the death rate to 8 percent. The death rate of 25 percent in 2001 was linked with the correct treatment of OIs in the hospital and the existence of a home care program; the death rate would probably have been higher in the absence of these factors. The reason that the death rate has fallen from only 25 percent to 8 percent is that most PHAs do not visit a hospital until they are already sick with advanced immune suppression: in patients taking ARV drugs, the median CD4 count at the time of initiation of ARV drugs was 26 cells per mm³.

After taking ARV drugs for one year, the leader of Tan Tanod became pregnant in 2003 and delivered healthy twin boys, to the delight of both herself and her husband. The new PHA leader (also on ARV drugs) has recently been employed by the hospital as a night guard, a good indication that AIDS is regarded in this hospital as a normal disease. It is unusual in Thailand for a hospital to give a leadership role to a known HIV-positive employee, in particular one who is open about his HIV status in the community. Other district hospitals in Petchburi province provide ARV drugs. The Thai

Effect of ART on HIV Transmission

Public policy makers need to consider not only the direct effects of ART policy on the patients receiving ART, but also the indirect effects of ART on the creation of new cases of HIV infection.⁸ Increasing evidence exists, for example, that the availability of ART may lead to complacency and increased risk behavior by people on ART and to negative and positive aspects of HIV in surrounding communities. (Dukers and others 2001; Stolte and others 2001; Van de Ven and others 2005). Assessing those spillover effects of ART on people other than the patients is an indispensable part of designing policy. Table 3.8 provides a classification of those indirect, or external, effects into biological and behavioral effects on transmission. Within each of the categories, the effects could be beneficial, by slowing transmission, or adverse, by accelerating it.

Network of PHA groups, MSF, and the provincial health department are working together to establish and strengthen PHA groups in the neighboring hospitals. One hopes that these groups can provide practical support for PHA benefiting from the wider access to ARV drugs.



Source: Wilson and Ford 2004, with help from Chatchai Lalong of Ban Laem Hospital, who provided statistics.

Reduces Infectiousness

Current discussions about the benefits of providing ART to populations in resource-poor countries focus on the ability of ART to reduce the quantity of virus in bodily fluids and therefore to reduce the risk of transmission (Vernazza and others 1999). On the basis of the observed reduction in viral load in blood plasma, experts have predicted that the infectiousness of an HIV-infected person on ART would be reduced by a factor of somewhere between two and eight. That is, the probability of transmission on a single sexual encounter would be reduced to somewhere between 12.5 and 50 percent of its normal value (Over and others 2004). However, evidence on the links between reduced viral load in the plasma and reduced transmission is mixed. Indeed, some recent studies have shown that active virus can be isolated from the genital tract even when there seems to be ade-

Table 3.8 Possible Effects of ART on HIV transmission

		<i>Direction of effect</i>	
		<i>Beneficial (slows transmission)</i>	<i>Adverse (speeds up transmission)</i>
<i>Type of effect</i>	<i>Behavioral</i>	<i>Reduced infectiousness:</i> ART may lower viral loads and may therefore lower the risk of transmission per sexual contact.	<i>Selection for resistance:</i> Imperfect adherence to ART selects for resistant strains of the virus, which can then be transmitted. <i>Longer duration of infectivity:</i> Greater longevity of HIV-infected people taking ART has the unintended negative consequence of increasing the period in which the patient can transmit the virus.
	<i>Biological</i>	<i>Encouragement of prevention, especially diagnostic testing:</i> ART may increase the uptake rates of prevention activities, particularly voluntary counseling and testing.	<i>Increased risk behavior:</i> People receiving ART and HIV-positive and HIV-negative people in the surrounding community may engage in more risky behaviors than they would if ART were unavailable.

Source: Over and others 2004.

quate control of the virus in the blood plasma (Taylor and others 1999; Zhang and others 1998). Several studies have described the concentration of various ART drugs in semen samples. Those studies indicate considerable variation in individual drug levels in semen and no constant relationship between the blood and semen levels.

ART-induced reductions in infectivity depend importantly on how early in the course of the illness PHAs begin therapy. Recent evidence suggests that transmission occurs disproportionately during the first weeks following infection, when most HIV-infected people are unaware of their serostatus (Pilcher and others 2001). However, ART will likely be initiated during the latter stages of the disease, as is recommended by the current WHO guidelines on scaling up of antiretroviral (ARV) drug therapy in resource-limited settings (WHO 2004b). The combination of those factors—residual virus in the genital track, potential for early high transmissibility, and late initiation of ART—could conspire to limit the preventive benefits of ART.⁹

Encourages Prevention

ART may increase incentives to use preventive services. That possibility is often cited as an argument for expanding the availability of ART in resource-poor countries. The argument is that the availability of effective treatment may encourage people to come forward for VCT. Higher VCT uptake rates would mean that more people would receive prevention counseling and that more HIV-positive people would be detected at an earlier stage of the disease. Those rates could also mean that people who are HIV positive and in need of treatment could start on ART earlier, rather than waiting until they are sick enough to have to access the public health system. However, the actual magnitude of this pro-prevention effect will be highly context specific and will depend on factors such as the size of the increase in the uptake, the risk characteristics of people receiving VCT, and the quality of counseling.

Part of the challenge of using ART as prevention is to encourage people with HIV to be tested early in their illness by attending VCT services, to link those services with ART management, and to ensure good adherence. In Thailand, substantial dissociation remains between VCT and ART management, each of which is the responsibility of different departments of the MOPH. Despite the effort to link those activities, the current focus is largely on expanding the coverage of ART by recruiting patients through the public health system rather than by stimulating the demand for VCT and early recruitment into ART. The scenarios developed in chapter 5 model the potential effect on the epidemic of those two alternative recruitment and expansion strategies.

Selects for Resistance

In the past few years, the accumulation of evidence derived from studies in industrial countries shows that even modest departures from adherence to ART regimens foster the development of drug-resistant strains of HIV. The presence of drug-resistant strains of HIV in individuals limits the available treatment options and can lead to treatment failure. On a population level, the transmission of resistant strains of HIV may reduce the benefits of an ART distribution program.

A study of 417 participants in four HIV-NAT studies, which included both ART-naive and treatment-experienced patients, showed

a rate of virological failure (detectable viral load while taking ART) of 7.8 percent per year of ART. In another cohort of 60 patients who had been exposed to dual therapy and had failed to adhere to it, the virological failure rate was 16 percent per year of ART (Duncombe 2004).

Increases Risk Behavior

Growing evidence shows that increased availability of ART, together with the perception that there is a “cure” for HIV disease, may lead to a relaxation of efforts to avoid risky behavior. Studies of men who have sex with men (MSM) in Europe and the United States point toward increased risky behavior, such as higher incidence of unprotected anal intercourse and multiple sexual partners (Marseille 2003; Stephenson and others 2003; Stolte and others 2001; Suarez and others 2001; Van de Ven, Kippax, and others 1999; Van de Ven, Rawstorne, and others 2002; Ven 2005).

Comparable evidence for heterosexuals and for MSM in developing countries is scarce. In Brazil, however, the Ministry of Health has pointed to decreased condom use in young MSM, which coincides with the introduction of free ART to all Brazilian citizens, as a factor behind the recent rise in HIV incidence (Over and others 2004). Similarly, a study on the demand for an AIDS vaccine in Thailand suggests that measures perceived to reduce the chances of getting AIDS, such as an effective vaccine, would be associated with negative changes in condom use and risk behavior (Suratdecha and others 2005).

Detailed Resource Requirements for ART

Costs of ART can be defined in many ways, such as costs to the public sector, to individual patients, and to the society. In evaluating the various policy options for expanding public provision of ART in Thailand, we adopt the perspective of and estimate the costs to the public sector. This section summarizes the various costs associated with providing ART and presents estimated costs of ART in Thailand.¹⁰ Average costs of ART per patient are estimated on the basis of types of treatment regimens (first-line and second-line therapies); modes of service delivery (public, augmented public, and private service delivery); and stages of the disease (asymptomatic and symptomatic HIV).

Specific components included in estimating average costs of ART per patient are as follows:

- ARV drugs, lab tests, and monitoring
- treatment of OIs
- PHA support.

Cost data were obtained from existing studies in Thailand, both published and unpublished, and from informal consultations with local and international experts.

Costs of ARV Drugs and Monitoring

Since the production of GPO-vir started in 2002, the GPO has been expanding its production capability and is currently producing five different generic ARV drugs in various forms, combinations, and strengths.¹¹ That rapid expansion of generic drug production by GPO has greatly affected both access and affordability of ART through NAPHA.

Table 3.9 summarizes costs of various regimens currently available and recommended by the MOPH and WHO in their treatment guidelines. The annual costs of ARV drugs vary significantly between first-line and second-line regimens, ranging from B 14,400 (US\$360) (using GPO-vir) to B 273,864 (US\$6,847) (using expensive protease inhibitors) per patient per year (Duncombe 2004; GPO 2004). The average cost of a first-line ART regimen is estimated at B 19,271 (US\$482) per patient per year, using the weighted average of three categories of ART drug regimens under the MOPH treatment guideline.¹² The average cost of a second-line regimen is estimated around B 270,000 (about US\$6,700) per patient, costing nearly 14 times more than the average cost of a first-line regime.

In addition to the cost of ARV drugs, significant costs are associated with providing and monitoring ART treatment. The costs of outpatient and inpatient services are not negligible as use of medical services increases at the time of initiating ART treatment. A recent study¹³ evaluating medical resource use for ART, conducted jointly by WHO-Thailand and the Center for Health Economics at Chulalongkorn University in Bangkok, estimated that the average cost of hospital

Table 3.9 Costs of ARV Drugs Per Patient by Types of Regimens in Thailand, 2004

ARV drugs	Monthly cost		Annual cost	
	B	US\$	B	US\$
<i>First-line regimens (MOPH guideline)</i>				
(1) Lamivudine + stavudine + nevirapine	1,200	30.00	14,400	360.00
(2) Stavudine + lamivudine + efavirenz	2,579	64.50	30,948	773.70
Zidovudine + lamivudine + efavirenz	3,819	95.50	45,828	1,145.70
Zidovudine + lamivudine + nevirapine ^a	2,400	60.00	28,800	720.00
(3) Stavudine + lamivudine + IDV/r	3,500	87.50	42,000	1,050.00
Zidovudine + lamivudine + IDV/r	4,740	118.50	56,880	1,422.00
Average cost	1,606	40.10	19,271	481.80
<i>Second-line regimens (WHO guideline)</i>				
Abacavir + didanosine + Lopinavir/ritonavir	22,822	570.60	273,864	6,846.60
Abacavir + didanosine + saquinavir/ritonavir	22,094	552.40	265,128	6,628.20
Average cost	22,458	561.50	269,496	6,737.40

Source: Bureau of AIDS, Tuberculosis, and Sexually Transmitted Infection, MOPH, 2004; Duncombe 2004; and GPO 2004.

Note: Costs of ARV drugs are based on the lowest prices available, either generic or branded drugs, in Thailand, as of September 2004. US\$1 = B 40.

a. The GPO is currently in the process of producing a fixed-dose combination of GPO-Z (zidovudine, lamivudine, and nevirapine). The cost of GPO-Z is approximately B 1,400 (US\$35) per month.

services (including outpatient and inpatient services, but excluding ARV drugs, lab tests, and OI medications) is about B 7,700 (US\$192.50) per patient per year in public hospitals, ranging from B 12,850 (US\$321.25) in university teaching hospitals to B 5,340 (US\$133.50) in community hospitals (Supakakunti and others 2004).

The cost of a CD4 test by standard flow cytometry varies from B 200 to B 800 (US\$5.00 to US\$20.00) with the median cost of B 500

(US\$12.50), depending on the institution and the volume of testing. The cost of an HIV RNA (viral-load) test is significantly higher, averaging about B 3,500 (US\$87.50) per test. A basic safety chemistry panel measuring serum glutamic oxaloacetic transaminase, creatinine, and glucose costs about B 100 (US\$25.00) (Duncombe 2004; Gold and others 2005). In addition to the routine monitoring tests, patients incur sets of screening tests (that is, CD4 counts and HIV antibody tests) before initiation of ART. Those initial screening tests cost about B 1,100 (US\$27.50) per patient.

Cost of OI Treatment

Before the introduction of NAPHA, treatment for OIs comprised the bulk of treatment costs in Thailand's national AIDS expenditure. Existing studies on OI treatment from Thailand were reviewed to estimate the average cost of OI treatment per patient. As discussed in an earlier section, more than 20 different infections are associated with severe immune depletion. Even though the costs of OI treatment vary significantly depending on the type of infection and available treatment options, certain types of infections are observed most often among symptomatic HIV patients. Among the most commonly observed OIs in Thailand are CMV, cryptococcal meningitis, PCP, and TB (Ratanasuwan 2004; Supakakunti and others 2004).

The average costs of OI treatments vary across the studies, ranging from US\$64 to US\$206 (B 2,560 to B 8,240), with the average cost of US\$151 (B 6,040) per patient. To normalize the costs of OI treatment across the studies, we have adjusted those costs by assigning the relative weights of the three most commonly observed OIs (cryptococcal meningitis, PCP, and TB) (see tables B.2 and B.3 in appendix B). Relative weights were calculated in accordance with the prevalence of OIs among AIDS patients in Siriraj University Hospital from 2002 to 2004. Table 3.10 summarizes the estimated annual costs of OI treatment per patient in Thailand.

Cost of PHA Groups

PHA groups have long played a major role in providing the care and support needed for HIV patients in Thailand. Many of the public hospitals under NAPHA work with PHA groups that provide counseling, information, home visits, and other supports to PHAs. One can expect

Table 3.10 Average Cost of OI Treatment per Non-ART Patient-Year in Thailand
2002 US\$: 1US\$ = B 40

Source		TB	PCP	<i>Cryptococcal meningitis</i>	Total cost
Honda and others 2002	Average cost	45.63	35.07	131.80	
	Weighted	20.99	10.30	32.49	63.77
Lertiendumrong, Yenjittr, and Tangcharoensathien 2004	Average cost	165.21	257.19	167.19	
	Weighted	75.99	75.50	41.21	188.46
Prescott 1995 ^a	Average cost	54.00	41.40	283.85	
Kongsin and others 2004	Average cost	158.55	72.45	453.30	
	Weighted	72.93	21.27	111.72	205.92
	Weighted	24.84	12.15	69.96	104.60
World Bank 1999	Average cost	120.15	47.66	499.35	
	Weighted	55.26	13.99	123.07	192.33

Note: Relative weights of 46.0 percent, 29.4 percent, and 24.6 percent are assigned to TB, PCP, and cryptococcal meningitis, respectively.

a. Price figures are updated using the 2004 drug prices in Thailand

that continuous care and support from PHA groups will become increasingly important in expanding public provision of ART, specifically by supporting patients in their adherence to ART. Success of community involvement in HIV/AIDS care through PHA groups and community-based organizations has been well documented in Thailand, although very little has been studied about their resource requirements and financial sustainability. With the help of MSF-Thailand, and drawing on its experience with PHA support groups nationwide, we obtained some preliminary estimates of the costs of PHA support to improve adherence. Those estimates suggest that providing PHA support to improve adherence costs B 3,120 (US\$78) per patient (see table 3.11). In other words, such support adds some 7 to 8 percent to the total cost of ART per patient per year (Masaki 2004; Masaki and others 2005)

Average Cost of ART per Patient

The annual cost of ART using first-line therapy is estimated at about B 33,700 (US\$843) per patient (see table 3.12). The costs of ARV drugs and lab monitoring equal nearly 60 percent of the total ART cost when first-line therapy is used, whereas the share of ARV drugs

Table 3.11 Annual Cost of PHA Support Groups per 200 PHA Groups, 2004

<i>Items</i>	<i>Annual cost</i>	
	<i>Baht</i>	<i>US\$</i>
<i>Management level</i>		
Capital items (buildings, vehicles, computers, and so forth)	98,924	2,473
Recurrent items (rents, staff salaries, training costs, maintenance fees, utilities, and so forth)	6,168,996	154,225
<i>PHA group level</i>		
Capital items (buildings, vehicles, computers, and so forth)	550	14
Recurrent items (rents, allowances for volunteers, training costs, transportation costs, utilities, and so forth)	166,500	4,163
Total	6,434,970	160,874
Total cost per PHA group	187,943	4,699
Total cost per PHA trained	62,648	1,566
Total cost per client supported	3,132	78

Source: Thai Network for People Living with HIV/AIDS (TNP+), AIDS Access Foundation, and MSF in Thailand 2004.

and lab tests rises to 95 percent of ART costs when patients are on second-line therapy.

To evaluate costs of various policy options, we have estimated the average costs of ART per patient by modes of service delivery (that is, public and augmented public), by types of drug regimens (first-line and second-line), and by stages of disease (asymptomatic and symptomatic HIV). Those costs are summarized in table 3.13.¹⁴

Table 3.12 Annual Cost per Patient by Types of Drug Regimens

<i>Cost items</i>	<i>Annual cost per patient</i>			
	<i>First-line</i>		<i>Second-line</i>	
	<i>B</i>	<i>US\$</i>	<i>B</i>	<i>US\$</i>
(1) ARV drugs	18,847	471.20	263,567	6,589.20
(2) Lab tests	1,210	30.30	1,210	30.30
(3) OI treatment	4,815	120.40	4,815	120.40
(4) Outpatient service	2,773	69.30	2,773	69.30
(5) Inpatient service	6,041	151.00	6,041	151.00
(6) ARV drugs and lab tests: (1) + (2)	20,057	501.40	264,778	6,619.40
(7) Hospital services: (4) + (5)	8,815	220.40	8,815	220.40
Total ART cost: (3) + (6) + (7)	33,688	842.20	278,408	6,960.20

Source: Supakankunti and others 2004.

Table 3.13 Average Costs of ART per Patient by Types of Service Providers, 2004
Baht

ART costs	Public				Augmented Public			
	1st line		2nd line		1st line		2nd line	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
ARV drugs								
1st-line (MOPH)	19,271	19,271			19,271	19,271		
2nd-line (WHO)			269,496	269,496			269,496	269,496
Monitoring and lab	7,824	8,568	978	1,722	7,824	8,568	978	1,722
OI Treatment (with ART)	0	4,546	0	4,546	0	4,546	0	4,546
Hospital services	2,400	8,374	2,400	8,374	2,400	8,374	2,400	8,374
OPD service	2,400	2,400	2,400	2,400	2,400	2,400	2,400	2,400
IPD service	0	5,974	0	5,974	0	5,974	0	5,974
PHA support group					166,500	166,500	166,500	166,500
Total ART cost/ person month	2,458	3,397	22,740	23,678	16,333	17,272	36,615	37,553
Total ART cost/ person year	29,495	40,758	272,874	284,137	195,995	207,258	439,374	450,637

Source: Supakankunti and others 2004.

Note: The presented cost per patient is an average cost of provincial and community hospitals.

Notes

1. For example, see the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study, which involved 13,030 patients, where the progression rate found a median time to AIDS of 11.0 years (95 percent confidence interval, 10.7–11.7) (CASCADE 2000).

2. According to the World Health Organization (WHO) treatment guidelines, a first-line regimen for HIV should consist of two drugs from the nucleoside reverse transcriptase inhibitor group and one from the nonnucleoside reverse transcriptase inhibitor group. The WHO recommends one of the following four triple-drug combinations for a first-line regimen: (a) stavudine + lamivudine + nevirapine, (b) zidovudine + lamivudine + nevirapine, stavudine + lamivudine + efavirenz, or zidovudine + lamivudine + efavirenz. The WHO recommends that patients shift from a first-line regimen to a second-line regimen if treatment failure occurs. To increase the likelihood of treatment success and to minimize the risk of cross-resistance, the second-line regimen will include at least two new drugs, with at least one from a new class. The WHO-recommended second-line regimen (WHO 2003) is as follows: (a) if stavudine or zidovudine fail, change to tenofovir disoproxil fumarate or abacavir; (b) if lamivudine fails, change to didanosine; and (c) if nevirapine or efavirenz fail, change to lopinavir/ritonavir or saquinavir/ritonavir.

3. The MOPH and the Population Council are now carrying out a more rigorous impact evaluation study of adherence under the National Access to Antiretroviral Program for People Living with HIV/AIDS, in the same Chiang Mai region.

4. GPO-vir comprises stavudine + lamivudine + nevirapine and is given in a dosage of one tablet twice daily. The quantity of stavudine is 40 milligrams twice daily if bodyweight exceeds 60 kilograms (GPO-vir S40) and is 30 milligrams twice daily if bodyweight is less than 60 kilograms (GPO-vir S30).

5. The 2NN study is an open-label comparative study to evaluate the antiviral efficacy and safety of using nevirapine and efavirenz or

both drugs combined in combination with stavudine and lamivudine. It was presented at the 10th Conference on Retroviruses and Opportunistic Infections, held in Boston on February 10-14, 2003.

6. David Wilson, MSF, personal communication, Bangkok 2005.
7. Personal communications with Chris Duncombe (Thai Red Cross/HIV-NAT), Julian Gold (Albion Street Clinic), and David Wilson (MSF), Bangkok 2005.
8. This discussion draws heavily from Over and others (2004).
9. Wawer and others (2005) provide data that support the reverse J-shaped pattern of infectivity with high initial infectivity, followed by low infectivity for many years before the onset of AIDS symptoms. They conclude that ART will have little effect on infectivity.
10. This section draws heavily from Masaki (2004).