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Early Antiretroviral Therapy for Patients With Acute AIDS-Related Opportunistic Infections: A Cost-Effectiveness Analysis of ACTG A5164

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Abstract

Purpose—ACTG A5164 demonstrated that early antiretroviral therapy (ART) in HIV-infected patients with acute opportunistic infections (OIs) reduced death and AIDS progression compared to ART initiation 1 month later. We project the life expectancies, costs, and incremental cost-effectiveness ratios (ICERs) of these strategies.

Method—Using an HIV simulation model, we compared 2 strategies for patients with acute OIs: (1) an intervention to deliver early ART, and (2) deferred ART. Parameters from ACTG A5164 included initial mean CD4 count (47/ μ L), linkage to outpatient care (87%), and immune reconstitution inflammatory syndrome 1 month after ART initiation (7%). The estimated intervention cost was \$1,650/patient.

Results—Early ART lowered projected 1-year mortality from 10.4% to 8.2% and increased life expectancy from 10.07 to 10.39 quality-adjusted life-years (QALYs). Lifetime costs increased from \$385,220 with deferred ART to \$397,500 with early ART, primarily because life expectancy increased, producing an ICER of \$38,600/QALY. Results were most sensitive to increased intervention cost and decreased virologic efficacy in the early ART strategy.

Conclusions—An intervention to initiate ART early in patients with acute OIs improves survival and meets US cost-effectiveness thresholds. Programs should be developed to implement this strategy at sites where HIV-infected patients present with OIs.

Keywords

antiretroviral therapy; HIV; cost; cost-effectiveness; opportunistic infection

Despite the widespread availability of potent antiretroviral therapy (ART) in developed countries, many individuals with HIV infection initially present to care with advanced immunodeficiency and AIDS-related opportunistic infections (OIs).^{1–3} To determine the optimal time to start ART in such patients, the ACTG A5164 trial compared 2 strategies: (1) ART initiation within 14 days of an OI diagnosis and within 48 hours of study enrollment (early ART), and (2) ART initiation at least 4 weeks after randomization (deferred ART). Median time from initiation of OI treatment to starting ART was 12 days in the early ART arm and 45 days in the deferred ART arm. The trial demonstrated a decreased risk of AIDS progression (ie, another AIDS-defining illness) or death among patients receiving early ART, with no increase in treatment failure, complications of therapy, or immune reconstitution inflammatory syndrome (IRIS).⁴

Although these results suggest that the benefits of early ART are clear, initiating ART upon diagnosis of an OI in these patients will require additional resources. In particular, patients with advanced AIDS-related illnesses who begin ART promptly will typically require an intervention from an HIV physician specialist, a nurse, and a case manager. Their roles may include selecting an appropriate ART regimen, carrying out a monitoring plan, and counseling patients about the critical importance of medication adherence and linkage to care. Using data derived from ACTG A5164, we seek to project the life expectancy, cost, and cost-effectiveness associated with an intensive intervention to provide early ART to HIV-infected patients presenting with OIs in the United States.

METHODS

Analytic Overview

We used a widely published model of HIV disease^{5,6} to project the short- and long-term survival and costs of treating HIV-infected patients who present to care with acute OIs in the United States. Patients initiated ART according to 1 of 2 strategies: (1) early, following an intensive intervention designed to provide early ART; or (2) 1 month later, after treatment of the OI.⁷ The target HIV-infected population had the same characteristics (age, gender, CD4 count, HIV RNA distribution, and presenting OIs) as the 262 ACTG A5164 study subjects who were followed at US, but not South African, study sites.⁴ We adopt a modified societal perspective and report quality-adjusted life expectancies⁸ and direct medical costs (expressed in 2008 USD) discounted at an annual rate of 3%.⁹

Model Overview

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model is a state-transition first-order Monte Carlo simulation of the natural history, clinical management, and costs of HIV disease.^{5,6} Patients make monthly transitions between “health states” that are defined by current CD4 count, HIV RNA level, history of OIs, and ongoing acute OIs. ART can lead to increased CD4 counts, reduced HIV RNA levels, ART-related toxicities, and IRIS. Death may be attributed to an acute OI (within 30 days of diagnosis), chronic HIV (history of OI or other HIV complication), or non-HIV-related causes. The model records the time spent in each health state, clinical outcomes, and lifetime costs from entry into the simulation until death. Model descriptions have been published elsewhere in detail.^{5,6,10}

In this analysis, all patients were diagnosed with HIV upon presentation to care with acute OIs, consistent with the trial. Patients assigned to early ART initiated therapy immediately

upon HIV detection and incurred an additional cost in the first month of treatment, which corresponded to the per-patient cost of an intervention to start patients on ART as quickly as possible. This intervention was modeled after the Rapid Response Teams in place at various hospitals throughout the United States, whose objective is to reduce hospital mortality by responding immediately to impending crises such as myocardial infarctions or strokes.^{11,12} Patients assigned to the deferred ART arm started routine HIV care, including ART, 1 month after OI diagnosis.⁴ They did not incur any additional intervention costs beyond OI treatment in the first month of therapy.

Input Data

Cohort characteristics—We used data from the combined US-based arms of ACTG A5164 to define the simulated cohort (Table 1).⁴ Mean age was 39 years and 88% of patients were men. Mean plasma HIV RNA was 5.66 log₁₀ copies/mL and mean CD4 count was 47/ μ L. The majority of patients (63%) presented to care with *Pneumocystis jirovecii* pneumonia (PCP). Other common OIs at presentation included non-PCP fungal infections (16%) and bacterial infections (12%).⁴ None of the simulated patients had active tuberculosis, as this was an exclusion criterion for ACTG A5164.⁴

Progression of HIV disease—We used data from the Multicenter AIDS Cohort Study for HIV-related mortality rates, the incidence of primary OIs, and monthly CD4 declines when patients were off ART or on failed ART.^{13,14} As in ACTG A5164, 7% of patients developed IRIS a median of 1 month after ART initiation.⁴ We assumed a cost (\$895)^{15–18} and quality of life decrement (11%) related to IRIS, but no mortality, as was the case in ACTG A5164 (see Table 1).⁴

Treatment characteristics—In ACTG A5164, the primary endpoint could be assessed for 87% of enrolled subjects in each arm. Thus we assumed that 13% of patients who entered the model could not be linked to care and did not accrue the benefits of either ART or OI prophylaxis (Table 1). Patients who were linked to care received CD4 count and HIV RNA tests every 3 months.⁷

Patients could receive up to 6 sequential ART regimens during the remainder of their lives (Table 1). Six months after ART initiation, 70% of patients were virologically suppressed, with HIV RNA <400 copies/mL. The efficacy of first-line ART was adapted from the regimens given to patients in ACTG A5164.⁴ Second-line ART consisted of ritonavir-boosted atazanavir and 2 nucleoside reverse transcriptase inhibitors (NRTIs).^{19,20} In the United States, genotypic resistance tests determine individualized regimens, so the sequences of ART regimens vary widely once patients start their third line of therapy. We therefore modeled subsequent lines of ART as standard regimens with decreasing ranges of efficacy, as represented by various recent studies.^{21–30} Patients switched ART regimens upon virologic failure, defined as an observed increase in HIV RNA for 2 consecutive months.⁷

Costs—An analysis of resource utilization among US-based ACTG A5164 patients showed that mean hospitalization rates were 1.62 days/patient-month (PM; 95% confidence interval [CI], 1.55–1.69) in the early ART arm, and 1.72 days/PM (95% CI, 1.65–1.80) in the deferred ART arm. Rates of hospitalization and emergency department visits did not differ significantly between arms. We therefore used identical resource utilization estimates for both arms. These inputs were derived from a larger cohort of patients enrolled in HIV Research Network sites for a total of 59,093 patient-months.³¹

As ACTG A5164 did not record cost data, we derived inpatient, outpatient, and emergency department visit costs from University Health System Consortium data and the medical literature, using previously published methods.^{15–17,31–33} On average, 1 inpatient day cost \$1,480 in the month of an acute OI and \$2,270 in the month of death from an acute OI, whereas 1 outpatient visit cost \$280 and 1 emergency department visit cost \$550. Other costs included \$1,430/month for first-line ART and \$1,740 to 4,000/month for subsequent ART regimens.

We assumed that the resources required for the early ART intervention would be at least 5% annual effort on the part of a physician, a registered nurse, and a case manager. Average annual salaries derived from Bureau of Labor Statistics data were \$167,270 for a physician, \$62,480 for a registered nurse, and \$46,320 for a case manager. Fringe benefits were an additional 43.2% of salaries, for a total intervention cost of \$19,770/year.³⁴ We assumed that with this amount of effort the team would have the capacity to see on average up to 1 patient per week. In the base case scenario, ART-naïve patients presented to care with acute OIs on average once per month, corresponding to caseloads seen at representative ACTG A5164 sites. With a frequency of 1 eligible patient per month, the up-front cost of the intervention was \$1,650/patient (\$19,770/year divided by 12); at higher frequencies the cost per patient was lower, due to economies of scale (ie, more patients seen for the same annual salary cost).

Sensitivity Analyses

We performed several sensitivity analyses on all major model parameters. We varied the per-patient intervention cost from the maximum capacity of 1 patient per week (\$380) to 1 patient every 5 years (\$98,870). We also assessed the impact of variations in CD4 count and OI distribution at presentation to care, rates of successful linkage to and retention in outpatient care, the delay from presentation to ART initiation among patients deferring ART, and the efficacy of first-line ART, IRIS incidence, and the assumption of no IRIS-related mortality among patients initiating ART early.

RESULTS

Model Calibration

We calibrated the model to ACTG A5164 by matching the mortality rates and CD4 count increases of the simulated cohorts with data from the trial. At 48 weeks, mortality in the trial and model projections were 9.9% and 9.9% in the deferred ART arm and 7.1% and 7.7% in the early ART arm (Figure 1). CD4 count changes from baseline were 187/ μ L and 184/ μ L in the deferred ART arm and 187/ μ L and 192/ μ L in the early ART arm.

Base Case Analysis

When patients presenting to care with acute OIs waited 1 month to initiate ART,⁷ estimated 1-month mortality was 2.7%; at 1 year, projected mortality was 10.4% (Table 2). Mean CD4 count increased from 47/ μ L to 235/ μ L at 1 year. Mean discounted life expectancy was 10.07 QALYs and mean discounted lifetime cost was \$385,220 per person.

With an intensive intervention to start patients on ART early, estimated mortality decreased to 1.5% at 1 month and 8.2% at 1 year. Mortality rates among patients who initiated ART early remained lower than for patients who deferred ART, and this benefit was projected to continue for at least 20 years. This long-term difference in survival is reflective of the high rate of early mortality in patients initially presenting with complications of AIDS, as well as the benefits of therapy for those who survive at least 1 year. Among those patients who deferred ART and survived at least 1 year, long-term survival was similar to patients who

initiated ART early. Mean CD4 count increased from 47/ μ L to 242/ μ L at 1 year. Discounted life expectancy was 10.39 QALYs and discounted lifetime cost of care was \$397,500. The cost-effectiveness ratio for early ART compared to the deferred ART strategy was \$38,600/QALY gained (Table 2).

Sensitivity Analyses

To evaluate the impact of major model parameters on the cost-effectiveness of early ART, we modified inputs individually over a range of plausible values. Figure 2 shows the impact of varying the number of patients presenting with OIs on the cost-effectiveness of the early ART intervention, due to economies of scale. If the number of eligible patients increased to 1 per week (\$380/patient), early ART had a cost-effectiveness ratio of \$34,400/QALY gained compared to deferred ART. If we assumed that only 1 eligible patient presented to care each year, corresponding to an intervention cost of \$19,770/patient rather than \$1,650/patient, the total cost of care in the early ART arm increased to \$415,860, for a cost-effectiveness ratio of \$95,900/QALY gained (Table 2). Early ART had an incremental cost-effectiveness ratio below \$50,000/QALY gained as long as at least 4 eligible patients presented to care each year. Only when 1 case every 2 years was eligible for the intervention did the cost-effectiveness ratio exceed \$100,000/QALY gained.

Variations in the virologic efficacy of first-line ART among patients initiating ART early also had an impact on the results (Figure 2). If we assumed that the efficacy of first-line ART for these patients was lower than for patients who deferred ART, because of the difficulty of adhering to a complex medical regimen or additional drug toxicities, the benefits of early ART decreased. When the proportion of patients who were virologically suppressed 6 months after initiating first-line ART decreased to 62%, compared to 70% in the deferred ART strategy, the cost-effectiveness ratio of early ART increased to \$122,900/QALY gained. If the efficacy of first-line ART decreased to 58%, early ART was no longer the preferred strategy because it was less effective and more costly than deferred ART (dominated) (Table 2).

If linkage to care rates were as low as 36%, as seen at 1 urban medical center,³⁵ mortality at 1 year increased from 10.4% to 21.6% when patients deferred ART and from 8.2% to 20.5% when patients initiated ART early. The overall benefit of early ART decreased to 0.17 QALYs, but the cost-effectiveness ratio remained the same at \$38,500/QALY compared to deferred ART. If concurrent treatment of the OI and HIV resulted in decreased linkage to therapy only among patients starting ART early, this strategy became less favorable. If the rate of linkage to care was 4% lower among patients starting ART early than in those deferring ART (83% vs 87%), the intervention reduced quality-adjusted life expectancy to 10.01 QALYs and costs to \$383,510 for patients initiating ART early, indicating both a worse outcome and a lower cost than the current standard-of-care (Table 2).

If we increased the incidence of IRIS and assumed IRIS-related mortality for patients starting ART early, survival and costs decreased but the cost-effectiveness ratio did not change substantially. For example, when the 1-month probability of IRIS among patients starting ART early was 13%, with a 14% mortality (derived from the upper 95% CIs in a South African study³⁶), quality-adjusted life expectancy decreased to 10.20 QALYs among patients initiating ART early compared to 10.07 QALYs for patients deferring ART. The cost-effectiveness ratio was \$39,900/QALY (Table 2). When mean CD4 count at presentation to care increased to 200/ μ L, early ART became less cost-effective at \$57,100/QALY gained because the risk of dying or acquiring OIs while waiting to initiate ART decreases with higher CD4 counts. Variations in the rate of retention in care, distribution of OIs at presentation to care, efficacy of later ART regimens, and mortality from acute OIs and IRIS had little impact on cost-effectiveness results.

DISCUSSION

The ideal time to start ART in patients presenting with HIV-related OIs has been an area of long-standing controversy in clinical practice.³ Although such patients have advanced immunodeficiency and a poor prognosis without ART, there are several potential disadvantages to early therapy. These include overlapping drug toxicities, drug-drug interactions between antiretrovirals and medications used to treat OIs, the potential for reduced adherence to ART due to polypharmacy, and an increased rate of IRIS.

Because of these concerns, the ACTG A5164 trial compared a strategy of early ART, starting within the first 2 weeks of OI diagnosis, versus a delay of at least 4 more weeks before ART initiation.⁴ The results of the trial demonstrated that early ART led to both clinical and survival benefits, with no significant reduction in antiretroviral efficacy and no increase in drug toxicity or IRIS. Even though the results of this trial may not be applicable to all patients with OIs, they nonetheless remain relevant for populations presenting to care with advanced HIV disease in the United States and other high-income countries.

The results of ACTG A5164 suggest that early ART provides clinical benefits to patients with acute OIs. Such a strategy will require increased resources. In this analysis, we modeled a multidisciplinary team involving input from an HIV physician specialist, a nurse, and a case manager. Their roles would be to select the optimal initial therapy, provide patient education on drug side effects and the importance of adherence, and develop a follow-up plan for both OI and long-term HIV treatment.⁷ Given the increased resources required for this type of intervention, we projected the survival gains and cost-effectiveness of early ART using a widely published simulation model of HIV disease and inputs from the ACTG A5164 trial.

The analysis suggests that at a baseline cost of \$19,770/year (consisting of 5% effort each from a physician, a nurse, and a case manager), an intensive intervention to initiate ART early in patients with acute OIs is both effective and an efficient use of health care resources. The cost-effectiveness ratio of \$38,600/QALY gained is well within the range of other interventions widely recommended in HIV care, including genotype resistance testing at baseline (\$31,900/QALY)³⁷ and at treatment failure (\$26,900/QALY)⁶ and testing for HLA-B*5701 in patients starting abacavir-based ART (\$39,700/QALY; all ratios inflation-adjusted to 2008 USD).^{10,17} Further, it is comparable to or lower than cost-effectiveness ratios reported for medical treatment of other advanced chronic diseases in the United States, such as guideline-recommended care for patients with diabetes mellitus and mixed dyslipidemia (\$52,200/QALY)³⁸ and hemodialysis for critically ill patients (\$158,200/QALY; all ratios inflation-adjusted to 2008 USD).^{17,39}

Clinical centers, however, may be reluctant to invest in the personnel and time required for an early ART intervention if the number of eligible patients is low. In this analysis, a strategy of early ART had an incremental cost-effectiveness ratio <\$50,000/QALY as long as at least 4 eligible patients presented to care each year. The cost-effectiveness ratio for early ART remained attractive even with a relatively low number of cases, because most of the increased cost of the early ART strategy is due to improved life expectancy. The cost of the intervention – \$19,770/year – is small compared to the overall cost of treating HIV during an individual patient's lifetime, recently estimated at \$452,200 in the United States (discounted, inflation-adjusted to 2008 USD).³¹ Implementing this intervention in such low-incidence settings may be challenging, however, from a hospital budget perspective. Conversely, the intensive early ART intervention will provide the greatest benefit at clinical centers that see the largest numbers of patients, which will likely be urban public and academic centers with a substantial proportion of low-income patients. HIV reporting data

by state suggest that new HIV diagnoses are concentrated in urban centers: in Georgia, for instance, AIDS diagnosis rates are highest in the greater Atlanta region.⁴⁰

The results of this analysis were sensitive to variations in virologic suppression rates among patients initiating ART early. Virologic efficacy was similar in the early and deferred arms of ACTG A5164 and other studies of early ART in patients with OIs.⁴¹ However, if a strategy of early ART were to reduce virologic suppression rates by as little as 12% at 6 months compared to deferred ART, then starting ART early would no longer be effective or cost-effective. This is because virologic failure forces patients to switch to subsequent lines of therapy that are less effective and more expensive than first-line treatment. In contrast, there was little change in cost-effectiveness results within plausible ranges of the cost of the intervention, CD4 count at presentation, the efficacy of later lines of ART, and ART-related toxicities.

Another potential concern about starting ART early in patients presenting with OIs is that psychosocial factors may make it difficult for such individuals to be successfully linked to care for follow-up. We found that lowering the linkage to care rate to 36%³⁵ reduced survival gains from early ART substantially, but if linkage to care decreased at the same rate in the deferred ART group, the strategy of early ART remained cost-effective. Implementing the intervention would be expected to improve linkage rates, because intervention personnel would choose appropriate ART regimens, closely monitor all patients, and counsel them about the critical importance of medication adherence and linkage to care.

The ACTG A5164 trial did not find a significant difference in rates of IRIS between the early and deferred ART groups. In fact, the rate of IRIS was slightly higher in the deferred group versus the early group (9% vs 6%). For some OIs, early ART may lead to more frequent and potentially more severe IRIS.⁴²⁻⁴⁴ However, 2 recent prospective studies on HIV-infected patients with cryptococcal meningitis did not show an increased incidence of IRIS with earlier ART.^{45,46} Furthermore, other studies have not found an association between IRIS and increased rates of mortality.⁴⁷ Nonetheless, even if we increased the 1-month probability of IRIS in the early ART group to 13% and associated it with a 14% mortality,³⁶ the strategy of early ART remained cost-effective.

There are several limitations to this analysis. First, patients with tuberculosis were excluded from the trial, so results cannot be generalized to these patients, for whom the risk of IRIS may be higher than in patients with other OIs.⁴² Second, critically ill patients were generally not enrolled in the trial, because written informed consent and ability to take oral medications were required. One retrospective analysis of patients in intensive care units in Brazil, however, found evidence of the benefits of early ART, even in critically ill patients.⁴⁸ Finally, the model projects long-term outcomes from short-term ACTG A5164 data. However, the model was calibrated to the results of the trial, which provided a largely representative sample of individuals presenting for care with acute OIs in the United States, and utilized longer term data from other published studies.

CONCLUSION

A strategy of early ART for patients presenting to care with acute OIs in the United States improves clinical outcomes and is highly cost-effective. These results are maintained through plausible changes in clinical assumptions, including the efficacy of ART, the incidence of IRIS, and the likelihood of linkage to care. In centers that see even moderate numbers of patients with acute AIDS-related OIs, programs should be developed to enable these individuals to start HIV therapy promptly.

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Conflicts of Interest

Dr. Sax has been a consultant for Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Tibotec, and ViiV. He has received grant support from Gilead, Merck, and Tibotec. Dr. Grant has received grant support from GlaxoSmithKline and Bristol-Myers Squibb. Dr. Zolopa is a consultant for Bristol-Myers Squibb, Gilead Sciences, Tibotec, and Pfizer and has received grant support from Merck, Bristol-Myers Squibb, Gilead Sciences, Pfizer, and VIRxSYS.

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Figure 1.

Survival at 48 weeks in the ACTG A5164 trial (♦ early; ▲ deferred) and model-projected 1-year survival associated with early antiretroviral therapy (ART) and deferred ART in HIV-infected patients presenting with AIDS-related opportunistic infections in the United States. The “no ART” strategy is for comparison purposes only.

Figure 2.

Two-way sensitivity analysis on the annual number of new patients presenting to HIV care with opportunistic infections, and the virologic efficacy of first-line antiretroviral therapy (ART) among patients initiating therapy early. The cost-effectiveness ratio compares early ART to deferred ART. In the base case scenario, the virologic efficacy of first-line ART was 70% in both strategies. Virologic efficacy is defined as the proportion of patients with HIV RNA <400 copies/mL 6 months after initiating ART. QALY = quality-adjusted life-year.

Table 1

Summary of input parameters for a model of early ART compared to deferred ART for patients presenting with AIDS-related opportunistic infections in the United States

Variable	Baseline value	Sensitivity analysis range	Reference
Mean age, years (<i>SD</i>)	39 (9)	—	(4) ^a
Male sex, % of patients	88	—	(4)
Mean CD4 count at presentation to care, / μ L (<i>SD</i>)	47 (61)	25–200	(4) ^a
Initial viral load (copies/mL), %			
>100,000	46.4	—	(4) ^a
30,001–100,000	38.7	—	
10,001–30,000	13.4	—	
3,001–10,000	1.2	—	
501–3,000	0	—	
≤ 500	0.4	—	
Opportunistic infections at presentation to care, %			
<i>Pneumocystis jirovecii</i> pneumonia	63	20–68	(4)
<i>Mycobacterium avium</i> complex	2	—	(4)
Toxoplasmosis	5	—	(4)
Cytomegalovirus	2	—	(4)
Fungal infections	16	9–59	(4)
Bacterial infections	12	—	(4)
IRIS			
Probability of developing IRIS in the first month of ART, %	7	7–13	(4, 36)
Quality of life decrement in the month of IRIS, %	11 ^b	—	(10)
Mortality from IRIS, %	0	0–14	(4, 36)
Cost of IRIS, 2008 USD	895 ^c	895–3,874	(15–18)
Number of eligible patients, /year	12	0.2–52	Assumption
Linkage to outpatient care, % ^d	87	36–87	(4, 35)
Delay in ART initiation among patients deferring ART, months	1	0–6	(4)
Frequency of clinic visits	Every 3 months	—	(7)
ART efficacy, % HIV RNA <400 copies/mL at 24 weeks (mean increase in CD4 count at 48 weeks, / μ L)			
First-line in trial ^e	70 (189)	58–70	(4)
ATV/r + 2 NRTIs	70 ^f (110)	—	(19, 20)
Third-line	58 ^f (121)	60–90	(19–23)
Fourth-line	65 (102 ^g)	50–70	(24–27)
Fifth-line	40 (121)	20–50	(28–30)
Sixth-line	15 (45)	10–40	(28, 30)
Treatment costs, 2008 USD			
Intensive intervention for providing early ART, /year ^h	19,770	380–98,870	(34)
Inpatient day without opportunistic infection or death	1,540 ⁱ	—	(15, 31)

Variable	Baseline value	Sensitivity analysis range	Reference
Inpatient day with opportunistic infection but no death	1,480	—	(15, 31)
Inpatient day in month of death due to opportunistic infection	2,270	—	(15, 31)
Inpatient day in month of death not due to opportunistic infection	2,440	—	(15, 31)
Outpatient visit	280	—	(17, 33)
Emergency department visit	550	—	(17, 33)
ART regimen costs, 2008 USD			
First-line in trial ^e	1,430	—	(49)
ATV/r + 2 NRTIs	2,050	—	(49)
Third-line	2,040	—	(49)
Fourth-line	2,630	—	(49)
Fifth-line	4,000	—	(49)
Sixth-line	1,740	—	(49)

Note: SD = standard deviation; ART = antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome; ATV/r = ritonavir-boosted atazanavir; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; USD = United States dollars.

^aUnpublished analysis.

^bIn the absence of data on the quality of life decrement associated with IRIS, we assumed it was similar to the quality of life decrement associated with mild hypersensitivity reaction.

^cWe assumed the cost of IRIS consisted of 2 comprehensive outpatient visits, computed tomography scans of the abdomen and pelvis, a complete blood count, a comprehensive metabolic panel, and a blood culture.

^dIn each arm of ACTG A5164, 12.8% of patients had no endpoint information. We used this as a proxy for the proportion of patients who were not linked to care.

^eIn ACTG A5164, LPV/r with 2 NRTIs was administered to 82% of patients in the early ART arm and 71% of patients in the deferred ART arm. NNRTI-based regimens with 2 NRTIs were administered to 11% of patients in the early ART arm and 16% of patients in the deferred ART arm.⁴

^fAt 48 weeks.

^gAt 24 weeks.

^hThe intervention consists of 5% effort each of a physician, nurse, and case manager (see Methods section for details).

ⁱThe monthly cost of hospitalization is higher when patients do not have opportunistic infections, because these patients are hospitalized for fewer but more resource intensive days than patients with opportunistic infections.

Model-projected outcomes of early ART compared to deferred ART in HIV-infected patients presenting with AIDS-related opportunistic infections in the United States

Table 2

	1-month mortality, %	12-month mortality, %	Life-years, undiscounted	QALYs, discounted	Lifetime costs, discounted ^a	Incremental cost-effectiveness ratio, \$/QALY
Base case results						
No ART	2.7	31.9	2.29	1.69	80,700	—
Deferred ART	2.7	10.4	17.67	10.07	385,220	36,300
Early ART	1.5	8.2	18.20	10.39	397,500	38,600
Sensitivity analyses						
52 eligible patients/year (intervention cost, \$380/patient)						
Deferred ART	2.7	10.4	17.67	10.07	385,220	—
Early ART	1.5	8.2	18.19	10.39	396,170	34,400
1 eligible patient/year (intervention cost, \$19,770/patient)						
Deferred ART	2.7	10.4	17.67	10.07	385,220	—
Early ART	1.5	8.2	18.22	10.39	415,900	95,900
Virologic efficacy of first-line ART in patients initiating ART early reduced to 58%						
Deferred ART	2.7	10.4	17.67	10.07	385,220	—
Early ART	1.5	8.7	17.45	10.05	393,350	Dominated ^b
36% linkage to outpatient care in early and deferred ART strategies ^c						
Deferred ART	2.7	21.6	9.77	5.75	227,010	—
Early ART	2.1	20.5	10.03	5.92	233,480	38,500
83% linkage among patients starting ART early						
Early ART	1.5	9.2	17.51	10.01	383,510	—
Deferred ART	2.7	10.4	17.67	10.07	385,220	26,400 ^d
1-month probability of IRIS in patients initiating ART early, 13%; probability of death from IRIS, 14% ^e						
Deferred ART	2.7	10.4	17.67	10.07	385,220	—
Early ART	1.5	10.0	17.86	10.20	390,340	39,900
CD4 count at presentation to care, 200 cells/ μ L						
Deferred ART	1.1	6.5	19.92	11.37	414,540	—
Early ART	0.6	5.9	20.08	11.47	420,220	57,200

Note: QALY = quality-adjusted life year; ART = antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome.

^a All costs are in 2008 USD.

^b Dominated: a strategy with a higher cost and an equal or lower quality-adjusted life expectancy than another strategy.

^c Reference 35.

^d In this sensitivity analysis, deferred ART leads to a longer projected life expectancy than early ART.

^e Upper 95% CI of IRIS incidence and mortality rates in a South African study.³⁶