

Setting Performance Standards for a Cost-Effective Human Immunodeficiency Virus Cure Strategy in South Africa

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Background. Reports of a single case of human immunodeficiency virus (HIV) eradication suggest that elimination of HIV from individuals is possible. Anticipating both increased research funding and the development of effective, durable cure technologies, we describe the circumstances under which a cure might improve survival and be cost-effective in South Africa.

Methods. We adapted a simulation model comparing a hypothetical cure strategy (“Cure”) to the standard of care, lifetime antiretroviral therapy (“LifetimeART”) among adherent South Africans (58% female; mean age 33.8 years; mean CD4 257/ μ L; virologic suppression ≥ 1 year). We portrayed cure as a single intervention, producing sustained viral eradication without ART. We considered both a plausible, more imminently achievable “Baseline Scenario” and a more aspirational “Optimistic Scenario”. Inputs (Baseline/Optimistic) included the following: 50%/75% efficacy; 0.6%/0.0% fatal toxicity; 0.37%/0.085% monthly relapse over 5 years (0.185%/0.0425% per month thereafter); and \$2000/\$500 cost. These inputs were varied extensively in sensitivity analysis.

Results. At baseline, Cure was “dominated,” yielding lower discounted life expectancy (19.31 life-years [LY] vs 19.37 LY) and greater discounted lifetime costs (\$13 800 vs \$13 700) than LifetimeART. Under optimistic assumptions, Cure was “cost-saving,” producing greater survival (19.91 LY) and lower lifetime costs (\$11 000) than LifetimeART. Findings were highly sensitive to data assumptions, leaving little middle ground where a tradeoff existed between improved survival and higher costs.

Conclusions. Only under the most favorable performance assumptions will an HIV cure strategy prove clinically and economically justifiable in South Africa. The scientific pursuit of a cure should not undermine continued expansions of access to proven, effective, and cost-effective ART.

Keywords. cost-effectiveness; cure; HIV; modeling; South Africa.

South Africa, home to approximately 20% of the world's 37 million people living with human immunodeficiency virus (HIV) [1], experiences both great successes and massive challenges in HIV treatment. Since antiretroviral therapy (ART) was first rolled out nationwide in 2004 [2], life expectancy for South Africans with HIV has increased dramatically [3]: total ART-attributable survival gains among the 2.2 million South Africans receiving treatment are estimated at 21.7 million life-years (LY) [2]. Yet, despite an annual investment exceeding \$1 billion in acquired immune deficiency syndrome (AIDS) programs [4], 3.2 million HIV-infected South Africans remain

untreated [5]. Even among those receiving state-of-the-art care, long-term clinical complications [6, 7] and social stigma persist [8]. In addition, although ART dramatically reduces HIV transmission risks [9], imperfect adherence and medication interruptions attenuate this effect [10]. Only 25% of HIV-infected South Africans have a suppressed viral load [11], and an estimated 470 000 new HIV infections occur annually [12].

Given the persistent challenges of containing and treating HIV infection—even in the presence of effective therapy—many observers argue that an effective and affordable cure is needed [13]. Reports of successful HIV eradication via allogeneic stem cell transplantation suggest that elimination of the virus from an individual is possible, even if that strategy still has not been replicated and is far from practicable [14]. In December 2013, President Obama recognized the magnitude of the opportunity by pledging \$100 million for cure research [15]. Between 2015 and 2016, the cure research budget of the US National Institute of Allergy and Infectious Diseases grew by \$21.6 million [15]. Most recently, an expert panel convened by the International AIDS Society (IAS) declared the development of a safe, affordable, and scalable cure strategy “a key priority” and identified

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modeling and decision analysis as important tools in understanding and optimizing cure performance [13].

The IAS call for model-based approaches to evaluate cure programs motivates the present analysis. The scientific challenge of transforming HIV cure from proof-of-concept to viable public health strategy is only one of many obstacles. A cure policy must compare favorably to existing standards of HIV care, in terms of its costs, benefits, and side-effects. Anticipating newer, more practical cure modalities, we sought to establish performance benchmarks, exploring how good an HIV cure would need to be to deliver longer survival, lower costs, and/or cost-effectiveness compared with currently available ART in South Africa.

METHODS

Analytic Overview

We conducted a model-based, “what-if” comparison of the clinical and economic performance of a theoretical HIV cure strategy (Cure) to the standard of care, lifetime antiretroviral therapy (LifetimeART), in highly adherent, HIV-infected South Africans who have been virologically suppressed for at least 1 year [16, 17]. We used the Cost-Effectiveness of Preventing AIDS Complications International (CEPAC-I) model, a Monte-Carlo microsimulation of HIV disease and treatment [2, 18, 19], to portray Cure as an intervention producing immediate and sustained elimination of the virus, with no detectable viral replication by standard HIV ribonucleic acid (RNA) assays. Model outputs included life expectancy and lifetime costs (2014 US dollars), reported both undiscounted and discounted to present value at 3%/year [20]. For purposes of economic evaluation, we calculated incremental cost-effectiveness ratios (ICERs), defining a strategy to be “cost-effective” if it conferred LY for less than \$13 200 (the 2015 South African per capita gross domestic product [GDP] in international dollars [21, 22]). We conducted sensitivity analyses on this threshold and a variety of other input parameters to elucidate the circumstances that might make Cure an attractive alternative to LifetimeART in South Africa.

Cost-Effectiveness of Preventing AIDS Complications-International Model

The CEPAC-I model is a patient-level microsimulation of HIV disease, treatment, and economic resource use [18, 19]. Individual patients are generated by random draws of characteristics from specified age, sex, CD4 count, and HIV RNA distributions. Human immunodeficiency virus natural history is modeled as a series of monthly transitions between health states characterized by CD4 count and HIV RNA. Without treatment, patients’ CD4 counts decline according to a viral load-dependent trajectory [23]. Patients are subject to age- and sex-specific, non-HIV-related mortality.

We assume that patients initiate ART according to World Health Organization treatment guidelines (ie, regardless of CD4 count) [16]. Patients receiving ART experience high

probabilities of virologic suppression and subsequent CD4 count increases, with the greatest CD4 gains occurring in the first 2 months [24]. Higher CD4 counts reduce opportunistic disease (OD) and HIV-related death risks. Patients face a small monthly probability of loss of treatment efficacy (which we label “late ART failure”), resulting in virologic rebound. Human immunodeficiency virus RNA and CD4 counts are monitored annually to detect such failure [25]. Per South African treatment guidelines [25], all patients with confirmed virologic rebound are switched to a second-line ART regimen. Costs of HIV treatment and care are assessed from the health system perspective.

A technical specification of the CEPAC-I model—including flowcharts, state space definitions, transition probabilities, code, data fields, protocols for data assembly, base parameter values/ranges/sources, sample output, and programming notes—is available at <http://www.massgeneral.org/mpec/cepac/>.

Cure Simulation

We simulated a hypothetical cure strategy (Cure), targeted (in conformity with planned or ongoing cure trials) to a population of highly adherent patients who have received suppressive first-line ART for at least 1 year [17]. We modeled cure as a one-time intervention producing sustained benefits for some proportion of patients. Patients initiating the Cure intervention were assumed to incur a one-time cost and were subject to both a one-time probability of successful viral eradication (beginning in the month after intervention) and a one-time probability of experiencing acute and potentially fatal toxicities. The model was able to simulate the incidence and duration of additional toxicities (eg, acute and chronic; fatal and non-fatal). Patients successfully and sustainably cured maintained undetectable viral loads while their CD4 counts increased and their risks of ODs were halved.

Patients were considered cured so long as an undetectable viral load was sustained without ART. However, cured patients faced a monthly probability of relapse, which triggered viral load rebound [26]. When relapse was detected (either through annual virologic monitoring or, less frequently, via presentation with an OD), patients were again placed on first-line ART followed by a second ART regimen, if virologic failure occurred. Cured patients continued to face monthly probabilities of non-AIDS mortality and to accrue costs for routine care and yearly CD4 and HIV viral load monitoring.

Model Inputs and Analysis

We used the CEPAC-I model to determine the distribution of CD4 counts in the Cure-eligible population. To perform this “initialization,” we constructed a cohort of ART-naive, HIV-infected South Africans presenting to care. This cohort was 58% female, with mean age 33.8 years (standard deviation [SD] 9.2 years), HIV RNA distribution with 46% >100 000 copies/mL, and mean CD4 count 257/ μ L (SD 118/ μ L) [2, 12, 27, 28] at ART initiation. All patients received first-line ART consisting

of efavirenz, tenofovir, and lamivudine or emtricitabine. After 1 year on suppressive ART, patients became eligible for the Cure intervention. Based on this initialization, we used a mean CD4 count of 418/ μ L (SD 121/ μ L) and HIV RNA below detectable levels for patients initiating Cure (Table 1).

The same initialization was used to generate the patient cohort for the standard-of-care comparator strategy, LifetimeART. To maintain a level playing field between the strategies, LifetimeART patients were also assumed to be highly adherent and responsive to treatment, fully suppressed for at least 1 year, with the same mean initial CD4. All patients in whom virologic rebound was confirmed (via annual HIV RNA monitoring and verbal confirmation of adherence) were switched to a second-line regimen, consisting of zidovudine, lamivudine, and lopinavir/ritonavir [25]. First- and second-line ART costs and efficacy (both standard and after Cure) are reported in Table 1.

Given the hypothetical nature of an HIV cure intervention, we considered a wide variety of input data values and assumptions. For the Baseline Scenario, we elected to portray Cure in a conservative light, choosing parameter values that might plausibly apply at the time of an initial rollout. We then constructed an Optimistic Scenario, reflecting more favorable aspirations about the future performance attributes of a proven and durable cure intervention. Finally, we explored an even broader range of possible data assumptions in extensive sensitivity analyses. For example, we assumed a 50% probability of cure success at Baseline, increasing that probability to 75% for the Optimistic Scenario, and exploring values ranging from 20% to 100% in sensitivity analysis. Likewise, we assumed a Baseline risk of fatal toxicity of 0.6% (reflecting the risks of strategies analogous to stem cell transplantation) at a cost of \$1027; for the Optimistic Scenario, we reduced the risk of fatal toxicity to 0%; and in sensitivity analysis, we considered risks

ranging from 0% to 5%. Toxicity rates and costs were estimated (and adjusted to reflect South African purchasing power) from observed experience with chemotherapy as a potential cure strategy in the United States [22, 29–32]. We assumed a Baseline relapse rate of 0.37%/month (Optimistic: 0.085%/month) for the first 5 years after Cure initiation, declining to 0.085% (Optimistic: 0.0425%/month) thereafter. Annual virologic (HIV RNA) and immunologic (CD4) monitoring were assumed to begin 12 months after the Cure intervention, analogous to current South African monitoring guidelines for virologically suppressed patients on first-line ART [25]. Because the cohort was weighted heavily toward highly adherent patients with sustained virological suppression on first-line ART, we assumed a 100% probability of virologic resuppression on ART at 48 weeks after failed Cure intervention, in both scenarios. At Baseline, we assigned Cure an immediate, one-time cost of \$2000 (Optimistic: \$500); we considered costs up to \$5000 in sensitivity analysis.

Sensitivity Analysis

We conducted a series of one-way deterministic analyses, varying salient Cure parameters to identify thresholds at which the intervention would become (or cease to be) “dominated” (ie, cost more and confer fewer LY), cost-effective (ICER < GDP per capita of South Africa [21, 22]), or “cost-saving” (cost less and confer greater survival) compared with LifetimeART. We also performed multiway, deterministic sensitivity analyses to assess the impact of simultaneous variation of those parameters identified as most influential in the preceding, one-way analyses. Finally, we conducted probabilistic sensitivity analysis (PSA) to understand the aggregate impact of uncertainty in a large number of input parameter values on our findings (Table 1 and Supplementary Material).

Table 1. Parameter Inputs for a Model-Based Analysis of a Potential HIV Cure in South Africa

Variable	Base Case (Range Examined ^a)	References
Baseline Cohort Characteristics		
Female subjects (%)	57.7%	[12]
Age, mean years (SD)	33.8 (9.2)	[27]
CD4 Count, Mean Cells/ μ L (SD)		[28]
Initial	257 (118)	
After initialization (suppressed for 1 year on ART)	418 (121)	
HIV RNA distribution before initialization (%)		[2]
>100 000 copies/mL	46	
30 001–100 000 copies/mL	33	
10 001–30 000 copies/mL	21	
<10 001 copies/mL	0	
Lifetime ART		
Standard efficacy (%suppressed at 48 weeks)	100	Assumption based on [29]
Efficacy after failed cure (%suppressed at 48 weeks)	100 (50–100)	Assumption
Probability of “late ART failure” monthly (%) ^b	0.1 (0.1–0.5)	Assumption
First-line (TDF+ “XTC” +EFV) ART cost, yearly (2014 USD)	136.80	[38]
Second-line (AZT+3TC+LPV/r) ART cost, yearly (2014 USD)	375.00	[38]

Table 1. Continued

Variable	Baseline Scenario	Optimistic Scenario	Range Examined in Sensitivity Analysis	References
Cure Characteristics				
Efficacy (%)	50	75	20–100	Assumption
Relapse rate monthly (%), ≤5 years	0.37	0.085	0–2.0 ^b	Assumption
Relapse rate monthly (%), >5 years	0.185	0.0425	— ^c	Assumption
Cure intervention cost (2014 USD)	500	2000	0–5000	Assumption
Fatal Toxicity Probability (%)	0.6	0	0–5.0	Assumption based on [29, 32]
Fatal Toxicity Cost (2014 USD)	1027	1027	—	Assumption
Acute Nonfatal Toxicity Probability (%)	6.0	6.0	—	[29, 31]
Acute Nonfatal Toxicity Cost (2014 USD)	50	50	—	Assumption based on [29, 30]
Chronic Nonfatal Toxicity Probability (%/month)	5.8	5.8	0–10.0	[29, 31]
Chronic Nonfatal Toxicity Cost, (2014 USD)	20, until switch to ART	20, until switch to ART	0–100	Assumption

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; RNA, ribonucleic acid; SD, standard deviation; TDF, tenofovir; USD, US dollars; XTC, lamivudine or emtricitabine.

^aParameter values for probabilistic sensitivity analysis were drawn from a uniform distribution that assigns equal likelihood to each of the possible values within the defined range.

^bLate ART failure: loss of treatment efficacy after sustained suppression on ART, resulting in virologic rebound.

^cThe monthly risk of relapse >5 years is always set at one half that of the ≤5-year risk.

RESULTS

Baseline Scenario

Using Baseline input values (Table 1), Cure had higher projected lifetime costs (\$13 800 vs \$13 700; \$22 600 vs \$23 500 undiscounted) and lower life expectancy (19.31 LY vs 19.37 LY; 33.08 LY vs 33.04 LY undiscounted) than LifetimeART (Table 2). In keeping with accepted practice, we label the Baseline Cure strategy dominated [20].

Optimistic Scenario

Under more optimistic assumptions (Table 1), Cure was cost-saving, yielding lower projected lifetime costs (\$11 000; \$18 700 undiscounted) and higher life expectancy (19.91 LY; 34.38 LY undiscounted) than LifetimeART (Table 2) [20].

One-Way Sensitivity Analysis

Varying each parameter across its plausible range (as specified in Table 1) while holding all other variables at their Baseline values

shed light on 3 parameters whose variability could cause the overall assessment of Cure to swing from dominated to cost-saving: (1) the monthly probability of loss of treatment efficacy after sustained suppression on ART (late ART failure, a proxy for poor adherence to ART over time [eg, treatment exhaustion]), (2) the efficacy of the cure intervention, and (3) the monthly probability of relapsing after the Cure intervention (Figure 1). For example, holding all other parameters at their Baseline values, Cure would cease to be dominated and become cost-saving if its efficacy rose from 50% to ≥60%. A third parameter, the cure cost, could cause the Cure strategy to be decrementally cost-effective (ie, saving money but with a survival loss) if set to the lowest extreme of its plausible range. Also notable was the general absence of any middle ground scenario in which the usual cost-effectiveness tradeoff was observed between greater survival and higher costs. With few exceptions, Cure was either unequivocally dominated or unequivocally cost-saving (Table 2).

Table 2. Cost-Effectiveness of a Hypothetical Cure Strategy in South Africa^a

Strategy	Discounted LY Gained	Discounted Costs (\$)	Incremental Cost-Effectiveness (\$/LY)	Cure Tipping Points ^b				
				Dominated ^c	Not Cost-Effective ^d	Decrementally Cost-Effective ^e	Cost-Effective	Cost-Saving
Baseline Scenario								
Lifetime ART	19.37	13 700	—					
Cure	19.31	13 800	Dominated					
Optimistic Scenario								
Lifetime ART	19.37	13 700	—	—	—	—	—	—
Cure	19.91	11 000	Cost-saving	—	—	—	—	—
Sensitivity Analysis on Baseline Scenario								
Fatal Toxicity Rate = 0.0%								
Lifetime ART	19.37	13 700	—	—	—	—	—	—
Cure	19.43	13 900	Cost-effective (ICER = 3300)	0.5%–1.5%	2.0%–5.0%	—	0%	—

Table 2. Continued

Strategy	Discounted LY Gained	Discounted Costs (\$)	Incremental Cost-Effectiveness (\$/LY)	Cure Tipping Points ^b				
				Dominated ^c	Not Cost-Effective ^d	Decrementally Cost-Effective ^e	Cost-Effective	Cost-Saving
Cure Efficacy = 70%								
Lifetime ART	19.37	13 700	—	—	—	—	—	—
Cure	19.53	13 300	Cost-saving	<60%	—	—	—	≥60%
Cure Relapse Rate = 0.2%/Month								
Lifetime ART	19.37	13 700	—	—	—	—	—	—
Cure	19.41	13 600	Cost-saving	>0.2%	—	—	—	≤0.2%
Cure Cost = \$500								
Lifetime ART	19.37	13 700	—	—	—	—	—	—
Cure	19.31	12 300	Decrementally cost-effective (ICER = 23 300)	>\$1500	\$1000–1500	<\$1000	—	—

Abbreviations: ART, antiretroviral therapy; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; Intl., international; LY, life-years.

^aBase case Cure assumptions: efficacy = 50%, cost = \$2000; relapse = 0.37%/month. Life years and costs are discounted at 3%/year.

^bSmall gaps in the ranges reported in these columns reflect the granularity created using discrete (rather than continuous) values for the sensitivity analysis.

^cDominated: The strategy produces reduced life expectancy and increased costs, compared with some combination of other strategies.

^dNot cost-effective: The strategy produces either (1) an increase in life expectancy and increased costs with an ICER > Intl. \$13200 (100% of 2015 South African GDP per capita), or (2) a reduction in life expectancy but yields offsetting economic savings with an ICER < Intl. \$13200.

^eDecrementally cost-effective: The strategy produces a reduction in life expectancy but yields offsetting economic savings [40].

We then conducted the same series of one-way sensitivity analyses, this time holding all other parameters at their Optimistic Scenario values (Figure 2). Under these more favorable general circumstances, we identified 4 parameters whose variability could cause the overall assessment of Cure to swing from cost-saving to “not cost-effective”: (1) cure fatal toxicity,

(2) the efficacy of ART after cure failure, (3) cure relapse, and (4) cure efficacy. For example, holding all other parameters at their Optimistic Scenario values, Cure would cease to be cost-saving if the risk of fatal toxicity rose from 0% to ≥3.0%; if that risk were to rise even further to ≥4.0%, Cure would cease to be cost-effective.

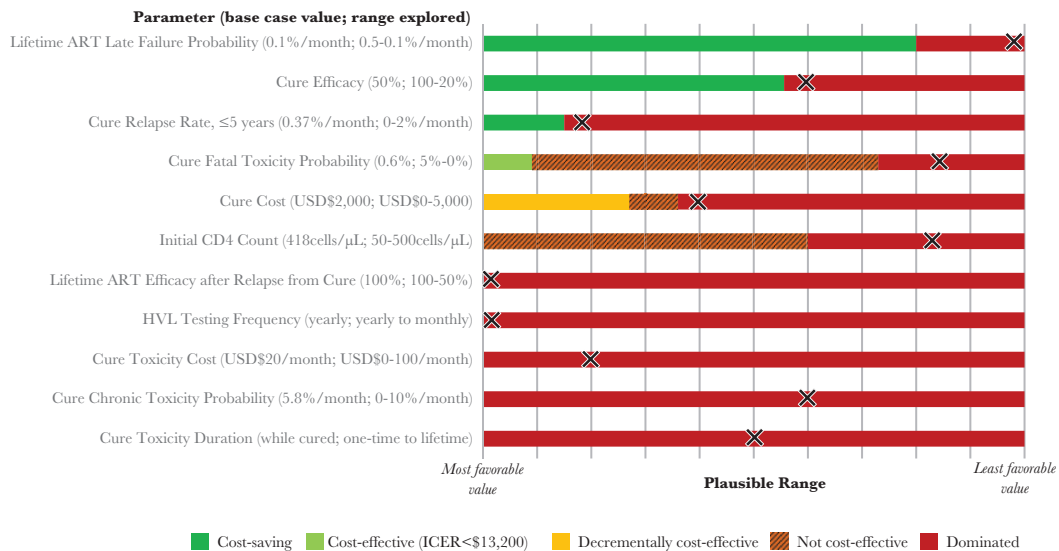


Figure 1. One-way sensitivity analyses of Cure (theoretical human immunodeficiency virus cure strategy) cost-effectiveness (Baseline scenario). The figure summarizes the results of a series of one-way, deterministic sensitivity analyses on the incremental cost-effectiveness ratio (ICER) of Cure compared with LifetimeART using Baseline scenario cure characteristics. Each horizontal bar represents the range of ICERs produced by varying a single model parameter across its plausible range, while all other parameters are held at their baseline values. The parameter inputs (listed along the vertical axis) are varied from their most Cure-favorable plausible value (left) to their least Cure-favorable plausible value (right). Red regions of the horizontal bars represent scenarios in which LifetimeART dominates Cure (ie, it costs less and results in higher life expectancy). Dark orange regions surrounded by dotted lines represent scenarios in which Cure is not cost-effective (ICER > 2015 gross domestic product per capita of South Africa). Yellow regions represent scenarios in which Cure is “decrementally cost-effective” (ie, saves money but with a survival loss). Green regions represent scenarios where Cure is cost-saving (ie, it costs less and results in higher life expectancy). For each parameter, a black ‘X’ indicates the location of the Baseline value within the plausible range.

Across a broad variety of one-way sensitivity analyses, some input parameters remained consistently uninfluential (ie, the overall assessment of Cure was unchanged as we varied them across their plausible ranges). These included the following: frequency of HIV RNA monitoring; monthly cost, probability, and duration of chronic nonfatal toxicity; initial mean CD4 count; and the cost-effectiveness willingness-to-pay threshold value.

Multiway Sensitivity Analyses

Figure 3A and B depict the sensitivity of the cost-effectiveness assessment to 3 of the parameters identified as most influential via one-way sensitivity analysis: (1) cure efficacy, (2) monthly probability of cure relapse at 5 years, and (3) cure cost. All other parameters are held at their Baseline (3A) and Optimistic (3B) Scenario values. The figures illustrate how delicately sensitive the overall assessment of Cure is to the input data. Under the highly optimistic assumptions of Figure 3B, Cure would probably be an attractive alternative to LifetimeART across plausible variants of the Baseline Scenario (Figure 3A), the conclusion that Cure would be dominated by LifetimeART is less unequivocal. Taken as a whole, the figures underscore the lack of middle ground: the boundary separating the zone of cost-ineffectiveness from the zone of cost savings is thin; for example, in the Baseline setting of Figure 3A and assuming a cure cost of \$2000, there are only 3 data scenarios under which Cure would be either

incrementally or decrementally cost-effective; in every other case, Cure would either be dominated or cost-saving, and the decision maker would not be forced to confront the usual tradeoff between cost and effectiveness.

Probabilistic Sensitivity Analyses

At willingness-to-pay thresholds of \$5700, \$13 200, and \$39 600/LY (representing 25%, 100%, and 300% of the South African per capita GDP in international dollars), LifetimeART would be preferred to Cure with probabilities of 89%, 90%, and 91%, respectively. (See Supplementary Material for more PSA inputs and results.)

DISCUSSION

An HIV cure strategy in South Africa would have to clear very high hurdles—in terms of efficacy, toxicity profile, durability, and cost—to compete with LifetimeART. Under conservative Baseline assumptions that might reasonably apply at the time of an initial rollout, we find that Cure is likely to be dominated by LifetimeART. We are able to construct a more optimistic scenario—one that emulates the 2 decades of experience with increasingly effective ART therapies and steadily improving HIV patient care—under which Cure becomes cost-saving. Moreover, we find little middle ground between these 2 extremes where the usual cost-effectiveness tradeoff between greater survival and higher costs is observed.

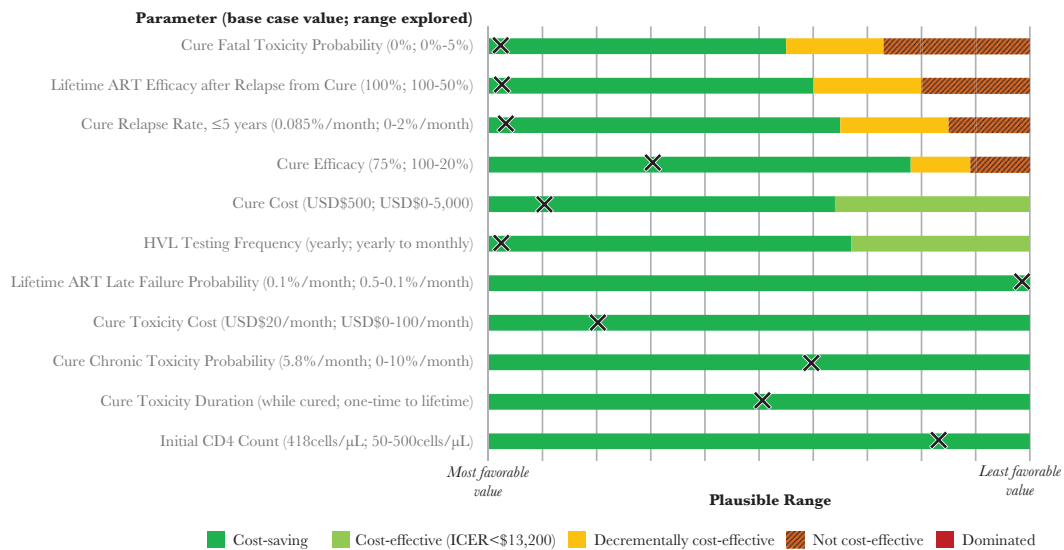


Figure 2. One-way sensitivity analyses of Cure (theoretical human immunodeficiency virus cure strategy) cost-effectiveness (Optimistic Scenario). The figure summarizes the results of a series of one-way, deterministic sensitivity analyses on the incremental cost-effectiveness ratio (ICER) of Cure compared with LifetimeART using more favorable Optimistic Scenario assumptions regarding Cure: 75% efficacy (up from 50%); 0.085% relapse risk (down from 0.37%/month for 5 years, 0.185% thereafter); 0.0% risk of fatal toxicity (down from 0.6%); and a cure intervention cost of \$500 (down from \$2000). Each horizontal bar represents the range of ICERs produced by varying a single model parameter across its plausible range, while all other parameters are held at their Optimistic Scenario values. The parameter inputs (listed along the vertical axis) are varied from their most Cure-favorable plausible value (left) to their least Cure-favorable plausible value (right). Red regions of the horizontal bars represent scenarios in which LifetimeART dominates Cure (ie, it costs less and results in higher life expectancy). Dark orange regions surrounded by dotted lines represent scenarios in which Cure is not cost-effective (ICER > 2015 gross domestic product per capita of South Africa). Yellow regions represent scenarios in which Cure is “decrementally cost-effective” (ie, saves money but with a survival loss). Green regions represent scenarios where Cure is cost-saving (ie, it costs less and results in higher life expectancy). For each parameter, a black ‘X’ indicates the location of the parameter value for the Optimistic Scenario within the plausible range. USD, US dollars.

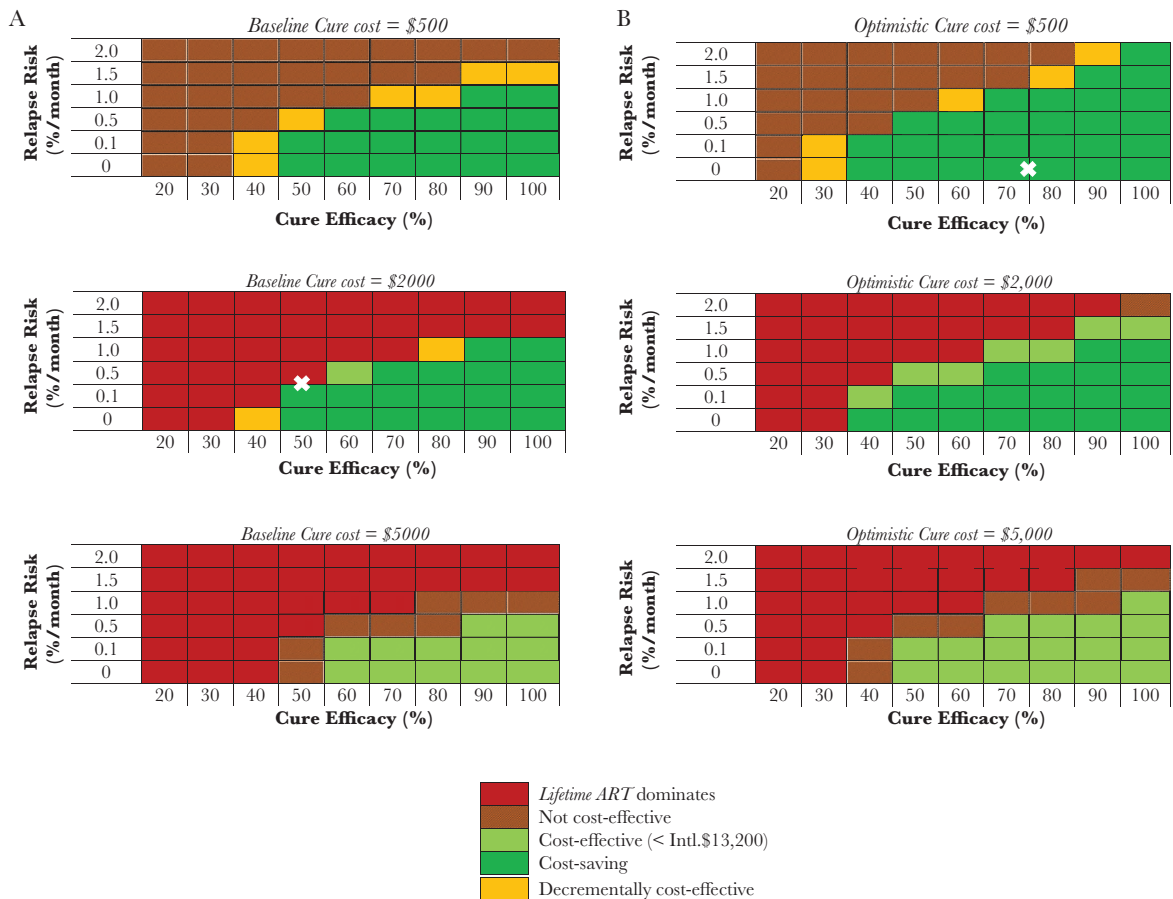


Figure 3. (A and B) Three-way sensitivity analysis of Cure (theoretical human immunodeficiency virus cure strategy) cost-effectiveness versus LifetimeART: Cure efficacy, relapse rate, and cost (Baseline/Optimistic Scenarios). The diagrams report the range of incremental cost-effectiveness ratios (ICERs) obtained when simultaneously varying 3 influential input parameters in the Cure intervention: Cure efficacy, 5-year monthly Cure relapse rate, and Cure cost. In each panel, the horizontal axis denotes Cure efficacy, whereas the vertical axis represents the monthly probability of relapse from Cure in the first 5 years after intervention. The panels represent 3 possible costs of Cure, ranging from \$500 to \$5000. All other parameters are held at their Baseline (A) and Optimistic (B) Scenario values. The shading represents the resultant ICERs, ranging from Dominance (ie, LifetimeART costs less and results in higher life expectancy than Cure) in red through Cost-saving (ie, Cure costs less and results in higher life expectancy than LifetimeART) in green. Yellow shading is used to denote situations where Cure is decrementally cost-effective (ie, saves money but with a survival loss). A white 'X' marks the situation where all parameters are set to their Baseline (A) and Optimistic (B) Scenario values.

Given the hypothetical nature of this investigation, readers should interpret our remarks less as a commentary on the prospects for better cure modalities (about which little is known) and more as a reminder that the urgent priority remains expanding the delivery of ART. Although the side effects and short-term potency of early HIV medications were readily endured during a time in which no other treatment was available, the advent of Cure would arrive in an era in which modern ART is unequivocally effective, remarkably well tolerated, and demonstrably cost-effective [19, 33]. Extending care to the more than 3 million HIV-infected South Africans who remain untreated will provide immediate individual and public health benefits. We note that global investments in HIV cure research increased 130% (from \$88 million to \$202 million) between 2012 and 2015, while overall international spending to address HIV in low- and middle-income countries declined 5% (from \$7.9 billion to \$7.5

billion) over the same period [34, 35]. Our analysis suggests that only the most promising cure strategies in this population will compete successfully—at least from a clinical and economic standpoint—with fully scaled-up, accessible ART.

This is not the first exploration of this question. Our research group previously assessed 3 potential cure strategies (chemotherapy, gene therapy, and stem cell transplantation), focusing on implementation in the United States [29]. As in the present analysis, we identified highly optimistic but plausible circumstances under which a cure might be cost-effective—and again, even cost-saving—by US standards, compared with current ART. However, the present analysis identifies different threshold values and sheds new light on the tradeoffs in South Africa, home to approximately 20% of the world's HIV-infected population. The results of this current analysis reflect the marked differences in the epidemic scale, cost structure, and national

ability to pay in South Africa versus the United States. In the United States, the annual cost of ART is \$40 000, implying a lifetime cost of HIV treatment of \$326 500 for patients infected at age 35 [36]; in South Africa, where ART costs are \$137–\$375/year and the estimated lifetime cost of care for a patient starting ART is \$16 360 [37, 38], a medically intensive, risky, and high-cost cure strategy is not a credible option.

A recently published analysis, conducted using data from Zimbabwe, reached different conclusions about the prospects for a cure [39]. Phillips et al [39] found that a 95% effective cure costing \$500 and producing rapidly declining rates of viral rebound would produce an 8.7% reduction in HIV program costs and avert 0.53 million disability-adjusted-LY (DALY) over 20 years. Using a cost-effectiveness threshold of \$500/DALY averted, the authors concluded that a cure intervention of this efficacy costing up to \$1400 would likely be cost-effective. Our Baseline Scenario portrays the Cure strategy less favorably: we are less optimistic about its efficacy, toxicity, durability, and cost; we are more concerned about the ongoing need to screen patients frequently for relapse; we are more optimistic about the uptake and performance of long-term ART; and we make no assumptions about increased risk-taking resulting from pre-exposure prophylaxis availability in the community and the adverse effects this might have on secondary HIV transmission. When we consider our Optimistic Scenario, relaxing our assumptions to more closely match those of Phillips et al [39], we arrive at an even more favorable conclusion: an effective and inexpensive cure is likely to be cost-saving. It will be critically important to update these assumptions as better data become available.

Our analysis raises but does not resolve issues regarding the target population for a cure. First, would it be ethical to focus a costly cure strategy on patients with well controlled HIV when millions of HIV-infected South Africans are not yet receiving treatment? Linking untreated, infected persons to effective ART would not only improve their personal health but would also avert secondary HIV transmissions [9]. By contrast, patients eligible for cure have already been virologically suppressed for at least 1 year and are likely to continue being adherent to their medications, virtually eliminating their risk of transmission. This question is beyond the scope of this paper but should be considered as cure research proceeds. Second, our analysis targets the cure strategy to patients who have successfully responded to and adhered to ART, maintaining virologic suppression for at least 12 months. Although focusing on such patients accurately reflects the eligibility criteria for ongoing cure trials [17], our portrayal may prove too pessimistic if future curative technologies are shown to work even in the presence of waning adherence or imperfect viral suppression.

This analysis has a number of important limitations. First, there is currently no proven cure strategy. All modeling and input data portraying cure are based on assumptions. We have

attempted to manage this limitation by conducting extensive sensitivity analysis. Readers should nevertheless interpret our what-if explorations as a benchmark-setting exercise that needs to be followed up with real-world comparative assessments. Second, this analysis does not account for the psychosocial benefits of being cured. Studies show that stigma, even among HIV-infected people on ART, decreases health-related quality of life [8]. By failing to account for the intangible (but nonetheless real) benefits of complete disease eradication, we may have undervalued cure. We do not consider the possibility of reinfection among those who are cured; practically, this would be similar to our sensitivity analysis that increases the likelihood of virologic rebound after a cure intervention. Finally, we have not included secondary HIV transmission effects.

CONCLUSIONS

Our findings suggest a 2-part policy response: first, focus on expanding access to ART for the 3.2 million HIV-infected South Africans who remain untreated; second, continue research to develop practical and affordable cure modalities. Until and unless an HIV cure can achieve a durable efficacy greater than 60% at a cost below \$2000, increased access to standard-of-care ART will be a preferred use of limited HIV resources in South Africa. Even a minimally acceptable HIV cure is not likely to be ready to be rolled out for decades. Given the magnitude of the South African AIDS epidemic and the observation that the current South African HIV detection and care strategy will be difficult to sustain without continued global partnerships, we conclude that pursuit of a cure should not divert resources or attention from expanding access to and improving the performance of ART.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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the editors consider relevant to the content of the manuscript have been disclosed.

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