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Identifying Key Drivers of the Impact of an HIV Cure Intervention in Sub-Saharan Africa

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Background. It is unknown what properties would be required to make an intervention in low income countries that can eradicate or control human immunodeficiency virus (HIV) without antiretroviral therapy (ART) cost-effective.

Methods. We used a model of HIV and ART to investigate the effect of introducing an ART-free viral suppression intervention in 2022 using Zimbabwe as an example country. We assumed that the intervention (cost: $500) would be accessible for 90% of the population, be given to those receiving effective ART, have sufficient efficacy to allow ART interruption in 95%, with a rate of viral rebound of 5% per year in the first 3 months, and a 50% decline in rate with each successive year.

Results. An ART-free viral suppression intervention with these properties would result in >0.53 million disability-adjusted-life-years averted over 2022–2042, with a reduction in HIV program costs of $300 million (8.7% saving). An intervention of this efficacy costing anything up to $1400 is likely to be cost-effective in this setting.

Conclusions. Interventions aimed at curing HIV infection have the potential to improve overall disease burden and to reduce costs. Given the effectiveness and cost of ART, such interventions would have to be inexpensive and highly effective.

Keywords. HIV; cure; economic evaluation; model; antiretroviral therapy.

Research is ongoing into developing an intervention that would allow human immunodeficiency virus (HIV)–infected individuals to have prolonged, and perhaps permanent, viral suppression in the absence of therapy ("remission" or "cure"). We refer to this as *antiretroviral therapy (ART)–free viral suppression* [1–8]. The implications of this research for sub-Saharan Africa, where most persons with HIV live, are as yet unclear, and any such intervention requires consideration in the context of resource-constrained public health approaches to treatment and prevention. Knowing what properties are likely to be required of such an intervention for it to be cost-effective or cost saving in low-income, high–HIV prevalence settings (ie, a "target product profile") is important to enable focusing of research, clinical development and delivery approaches.

In the current study, we sought to identify some basic product and delivery attributes within a framework of a global policy agenda. We addressed the following research questions. First, what would be the predicted impact of an intervention to induce sustained ART-free HIV suppression in low-income countries in sub-Saharan Africa, in terms of death rates, HIV incidence, and disability-adjusted life years (DALYs)? Second, under what conditions, particularly those relating to efficacy and cost, would such an intervention represent a cost-effective approach, within the context of continued expansion in access to ART?

METHODS

Model and Context

We assess these questions in the context of a generalized HIV epidemic with ongoing ART rollout using a model that has been informed by, and calibrated to, data from Zimbabwe [9–19]. We used the HIV Synthesis transmission model, an individual-based stochastic model of heterosexual HIV transmission, progression, and treatment in adults that has been described elsewhere ([20–23]; see Supplementary Material). Each simulation run generates time-updated longitudinal "data" over time for a population from 1989, such that the overall characteristics in terms of age, sex, sexual risk behavior, and HIV status resemble those of the entire adult population of Zimbabwe (HIV positive and negative). Transmission of HIV is modeled, with the HIV status of each (condomless sex) partner being sampled, along with viral load status of HIV-positive partners. For persons who have become infected with HIV, the variables for

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which longitudinal data are simulated include viral load, CD4 cell count, presence of resistance mutations, diagnosis status, linkage to care, maintenance in care and on treatment, and occurrence of AIDS and death.

Evaluation of the impact of an ART-free viral suppression (AFVS) intervention depends on the predicted outcomes in the absence of such an intervention and, in particular, the projected long-term effects of ART. The first-line regimen is assumed to be a combination of efavirenz, lamivudine, and tenofovir, and the second line regimen, ritonavir-boosted atazanavir, zidovudine, and lamivudine. It is assumed that no third line will be available. Table 1 presents the modeled 10- and 20-year outcomes after the start of ART. These outputs reflect model assumptions regarding adherence patterns, resistance acquisition, effect of adherence and resistance on virologic outcome and CD4 cell count changes, and the rate of interruption of ART and of ART toxicity, as detailed elsewhere (Supplementary Material; [17, 24–29]).

We initially concentrate on a base-case analysis and then consider a number of sensitivity analyses (Supplementary Table 1). We assumed that rates of HIV testing and hence ART coverage will continue to rise, although by lower amounts than in the last 5 years and that the policy will be for ART initiation in persons with CD4 cell counts <500 cells/μL and option B+ for pregnant women from 2015. Viral load monitoring of those receiving ART is assumed to start from 2015 onward. We also assume a modest increase in levels of condomless sex, such that HIV incidence is projected to decline only modestly (Supplementary Figure 2*D*). We assume continuation of trends in male circumcision uptake and no introduction of preexposure prophylaxis.

Table 1. Model Outputs of Status in 2025 and 2035 for Persons Starting ART in 2015[a]

Outcome	Persons Starting ART in 2015, %	
	10 y After Start of ART (2025)	20 y After Start of ART (2035)
On ART with VL <1000 copies/mL	53	31
On ART with VL >1000 copies/mL	6	3
Alive but off ART	9	5
Dead from HIV disease	20	40
Findings in those alive on ART[b]		
ART toxicity	37	34
Receiving second-line ART	24	37
NNRTI drug resistance	44	56
Resistance to NNRTI, NRTI, and PI classes	1	2

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

[a] These outputs reflect model assumptions regarding multiple aspects, including adherence patterns, resistance acquisition, effect of adherence and resistance on virologic outcome and CD4 cell count changes, and the rates of interruption of ART and ART toxicity. Full details of the modeling are given in the Supplementary Material, along with details and comparison of outputs for adherence, virologic outcome, NNRTI resistance, and ART discontinuation [20–29]; see references 20–23 for additional details.

[b] Percentages in this grouping represent proportions of those alive on ART.

AFVS Intervention

We envisaged an intervention that would induce AFVS, either by activating and killing latently infected cells and thus depleting the reservoir to zero or close to zero or by enhancing long-term immune control of a durable reservoir, with or without reservoir reduction. We assume that the intervention is introduced in 2022 and that 90% of persons in the country would have access to the intervention should they fulfill the eligibility criteria (50% in sensitivity analysis, which is perhaps more realistic if the intervention requires intravenous administration). We assume that the eligibility criteria for the intervention is an undetectable viral load for ≥6 months and a CD4 cell count >500 cells/μL. We consider that an AFVS intervention would most likely be started in those in whom ART had initially been used to reduce replicating virus. We assume that the AFVS intervention would be administered for 6 months (while ART is continued).

We assume that 95% of those given the AFVS intervention will be judged to have had a sufficient response to be able to stop ART. We then assume that failure—defined as a rebound in viremia—will occur initially at a rate of 0.05 per year in the first 3 months (eg, the probability of rebound is 0.05/4 in the first 3-month period), which declines thereafter by 50% per year (so, for example, the probability of rebound in the second 3-month period is $0.05 \times 0.5^{0.25}$; this equates to approximately 8% of persons having viral rebound by 5 years after interruption of ART; see Supplementary Figure 1). Viral load and CD4 T-cell count dynamics during AFVS failure were assumed to be comparable to those of an ART interruption. During periods of AFVS, we assume that the CD4 cell count will continue to

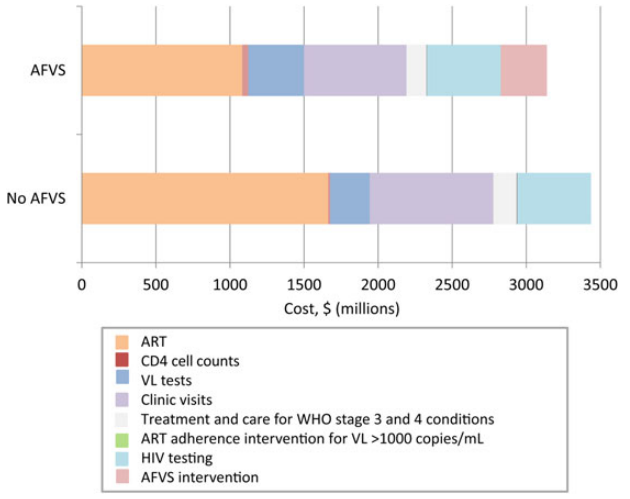

Figure 1. Overall program costs (in $m over 20 years; 2022–2042) according to whether or not the antiretroviral therapy (ART)–free viral suppression (AFVS) intervention is introduced (discounted at 3% per annum from 2015). Abbreviations: HIV, human immunodeficiency virus; VL, viral load; WHO, World Health Organization.

improve, as is the case with continued viral suppression during ART. We also assume that CD4 cell count– and age-specific morbidity and mortality rates will be no different from those in persons receiving ART with viral suppression, including that there remains some residual excess risk over and above that in the uninfected population (1.3-fold excess risk assumed; 1.0- and 1.7-fold considered in sensitivity analysis) [30–32]. We also consider in sensitivity analysis that the excess risk is 1.3-fold (and in a further sensitivity analysis that it is 1.7-fold) for persons receiving ART with viral suppression and 1.0-fold for those with AFVS.

We assume that individuals who have received the AFVS intervention will be monitored with viral load tests every 3 months for the first 5 years after ART interruption, and annually thereafter (as opposed to the annual monitoring throughout for persons receiving ART). This is to try to ensure rapid identification of viral rebound if it occurs. We further assume that individuals with ongoing AFVS are susceptible to superinfection, which will lead to viral rebound, whereas those receiving ART are assumed to not have risk of superinfection, owing to the protective effects of ART.

Consequences of disengaging from care are different for persons receiving ART and those with AFVS. For the former, adherence to regular care/drug pick-up is essential for continued viral suppression. In contrast, for those who have successfully achieved AFVS, disengagement from care does not have negative consequences unless and until viral load rebound occurs. Those receiving ART who experience viral rebound will be eligible to be switched to the second-line regimen; the rate of switch in such circumstances is 20% per 3 months once the above failure criteria are met. Those receiving the AFVS intervention are assumed to be given a maximum of 1 round.

Main Outcomes and Economic Analysis

The time perspective of the analysis was 20 years (2022–2042). The main outcome is DALYs for individuals aged 15–65 years. The DALY is a measure of overall disease burden. Persons incur a fraction of a DALY for each period of time lived with a disability, and a whole DALY for each year in which they have died but would still be younger than 65 years had they lived. Only HIV- or ART related disability is considered. The analysis was from a health systems perspective. We consider DALYs and costs in the whole population, not just those with HIV, and effects of transmission are accounted for.

A one-off cost of the AFVS intervention of $500 ($200 and $2000 in sensitivity analyses) is assumed (including cost of viral load testing HIV in the time before, and the first few weeks after, ART interruption). The cost of clinic visits during AFVS success is assumed to be $10 per 3 months ($5 in a sensitivity analysis), compared with $20 for persons receiving ART [33]; the cost is assumed to be lower because the person is not receiving ART. The current annual per-person cost (including supply chain) of ARVs is assumed to be $144 for the first-line and $312 for the second-line regimen [34].

The degree of disability experienced by a person, which is relevant in calculation of DALYs, is measured on a scale of 0 (no disability) to 1 (equivalent to death). We assume a toxicity of the intervention that results in a disability weight of 0.25 for the 6-month period of the intervention, but no increased mortality risk. A weight of 0.25 is approximately that estimated for severe diarrhea, acute low back pain, or acute gout, for example [35]. The disability weight due to living with diagnosed HIV is taken as 0.1 [36]. This is removed in those with ongoing AFVS success.

The cost-effectiveness threshold for a country represents the opportunity costs of resources required to fund the intervention, in terms of the health gains those resources could generate if used for alternative purposes in the public health care system [37]. As such, the threshold for a country is not readily apparent, but $500 per DALY averted is likely to be at the upper end based on the magnitude of benefit were resources spent on other programmatic priorities, such as eliminating coverage gaps for ART, if these are large [38], reflecting competing calls on HIV and non-HIV health care resources. This is just more than half of gross domestic product per capita [39]. DALYS, life years, and costs were discounted from 2014 values at 3% per annum. The AFVS intervention is considered cost saving (or "dominant") if it results in fewer DALYs and lower cost, and cost-effective if it results in fewer DALYs and increased costs but the cost per DALY averted is <$500.

RESULTS

The characteristics of the simulated population of Zimbabwe in 2014 and 2020 are shown in Table 2. Given assumptions that rates of testing will increase at a moderate rate and that ART initiation will be at CD4 cell count >500 cells/μL and with adoption of option B+ for pregnant women, the proportion of persons with an HIV diagnosis, and the number receiving ART is projected to increase. As a result of these assumptions, approximately 300 000 individuals aged 15–65 years are projected to be both eligible for, and have access to, the AFVS intervention in 2022 (26% of the entire HIV-positive adult population in the country at that time).

The proportion of persons who will receive the AFVS intervention is expected to rise to 65% in 2042 (Supplementary Figure 2*A*). The number with ongoing AFVS (Supplementary Figure 2*B*) is projected to approach a maximum of 550 000 by the early 2030s. The incidence of AFVS failure (viral rebound) is highest soon after the AFVS program is launched because many will access the therapy when it first becomes available, and most failures occur early (Supplementary Figure 2*C*).

The incidence of HIV infection is projected to decline with or without the AFVS intervention (owing to enduring effects of earlier reductions in condomless sex in the mid 1990s and

Table 2. Characteristics of the Simulated Population of Zimbabwe in 2014 and 2020

Output	2014	2020	Observed Data
Population aged 15–65 y	7 971 000	8 946 000	8 000 000[a]
Persons tested for HIV (per 3 mo), No.	687 000	882 000	2 274 328 aged 15–49 y tested in 2013[b]
Proportion of men circumcised (aged 15–65 y)	0.27	0.46	0.26 in men aged 15–29 in 2014[c]
Incidence of HIV (per 100 person-years) in persons aged 15–65 y	0.99	0.61	0.98 in 2013[b]
Prevalence of HIV in persons aged 15–49 y	0.14	0.11	0.15 in 2011 DHS[d]
Persons living with HIV, No.	1 167 000	1 124 000	. . .
Of persons with HIV, proportion diagnosed	0.84	0.91	. . .
Persons on ART (aged 15–65 y), No.	678 000	801 000	Approximately 700 000 on 1 January 2015[e]
Of persons with HIV diagnosis, proportion ever starting ART	0.75	0.87	. . .
Of persons with HIV diagnosis, proportion on ART	0.58	0.78	. . .
Death rate (per 100 person-years) in whole adult population aged 15–65 y	1.81	1.57	1.15 in persons aged 15–49 y[d]
Death rate (per 100 person-years) in persons with HIV aged 15–65 y	5.45	4.54	. . .
Death rate (per 100 person-years) in persons on ART aged 15–65 y	4.13	3.20	. . .
Of persons on ART, proportion with VL <500 copies/mL	0.81	0.84	0.78[f]
Of persons who ever started ART, proportion who started 2nd-line regimen	0.05	0.19	<0.02[e]
Of persons with HIV, proportion with VL >500 copies/mL	0.52	0.39	. . .
Of persons who ever started ART, proportion in whom 1st-line regimen has failed	0.13	0.24	. . .

Abbreviations: ART, antiretroviral therapy; DHS, Demograhic and Health Survey; HIV, human immunodeficiency virus; VL, viral load.

[a] Data from the Central Intelligence Agency [15].

[b] Data from UNAIDS [16].

[c] Data from Population Services International, Zimbabwe (personal communication).

[d] Data from the Zimbabwe National Statistics Agency (ZIMSTAT) and ICF International [18].

[e] Unpublished data (J. M.).

[f] Baseline results from the Sisters ART Programme for Prevention of HIV—an Integrated Response (SAPPH-IRe) trial [19]. Also, estimate of 0.90 reported in ref [17].

effects of viral suppression with ART), but it is projected to be somewhat lower with the AFVS intervention (Supplementary Figure 2*D*). Likewise, the prevalence of HIV infection (wherein persons with ongoing AFVS success remain classified as HIV positive) is projected to decline regardless of introduction of the AFVS intervention, but slightly more rapidly with the intervention (Supplementary Figure 2*E*). The number receiving ART will decline to <700 000 by 2042 without the AFVS intervention, and be <400 000 if the intervention is introduced (Supplementary Figure 2*F*).

The overall proportion of persons with HIV with an unsuppressed viral load (>500 copies/mL) is projected to decline only slowly from the level of 40% in 2022 without the AFVS intervention but to decline to close to 25% with introduction of the intervention (Supplementary Figure 2*G*). The death rate in those with HIV infection is projected to be lower with the AFVS intervention by about 0.5 per 100 person-years (8.4% lower; Supplementary Figure 2*H*). DALYs (discounted) will be slightly lower with the AFVS intervention (Supplementary Figure 2*I*). Costs are higher with the intervention in the initial few years after introduction owing to the intervention itself but lower thereafter, largely because fewer persons will be receiving ART (Supplementary Figure 2*J*). Further outputs are shown in Supplementary Figures 2*K*–*BD*.

With regard to projected costs, the main differences between the scenarios with or without AFVS intervention are the cost of ART, the cost of the AFVS intervention, the cost of clinic visits (less expensive in those with suppression), and the cost of viral load tests (done more frequently in persons with AFVS) (Figure 1). The AFVS intervention results in 539 738 DALYs being averted (252 215 life years gained), which equates to an average 2.6% reduction in death rate in the whole population aged 15–65 years (Table 3). The AFVS intervention also results in a cost reduction of $298 million (discounted), which represents an 8.7% reduction in the total budget over that period.

We also explored the effect of variations in assumptions on the DALYs averted with the AFVS intervention (Supplementary Figure 3). Assumptions about the degree to which ART is

Table 3. Discounted DALYs and Costs Over 20 Years (2022–2042) With or Without ART-Free Viral Suppression Intervention (Base Case)

	AFVS Intervention	
DALYs and Costs	Yes	No
DALYs	46 610 496	47 150 234
DALYs averted[a]	539 738	. . .
Costs, $ (in millions)[b]	3 139	3 437
Increment in costs, $ (in millions)[a]	-$298	. . .

Abbreviations: AFVS, ART-free viral suppression; ART, antiretroviral therapy; DALYs, disability-adjusted life years.

[a] Compared with no AFVS intervention.

[b] There is an 8.7% reduction in costs with AFVS intervention.

expected to be durably successful affect the magnitude of benefit of the AFVS intervention. In particular, when we assume a higher rate of interruption of ART (such that only 63% of ART experienced persons have a viral load <500 copies/mL, compared with 73% in the base case), the intervention benefit is greater. The benefit of the AFVS intervention is also greater if we assume that the rate ratio compared with the HIV-negative population for the non-AIDS mortality rate in persons with AFVS success is 1.0, but is higher (at 1.3- or 1.7-fold) for those with viral suppression during ART. If the disability weight from ART toxicity is assumed to be 0.15 rather than 0.05, then the impact of the AFVS intervention is again greater.

Figure 2 presents the cost-effectiveness of the AFVS intervention according to variation in combinations of key uncertain parameters of AFVS efficacy and access and cost parameters. The most strongly influential of these factors for cost-effectiveness is the cost of the AFVS intervention, with the efficacy of the intervention (degree of reduction in the viral rebound rate from the initial rate of 0.05 per year) also influential. In the context of the base case, the threshold cost of the AFVS intervention to be cost-effective is $1400, and the threshold to be cost saving is $975. If the AFVS intervention efficacy is lower, such that the percentage reduction in viral rebound rate per year is instead 20%, then the threshold cost of the AFVS intervention is $1000 to be cost-effective and $700 to be cost saving.

DISCUSSION

In this modeling and economic evaluation we have assessed what properties an intervention aimed at HIV cure should have for it to represent a cost-effective option in low-resource settings. The

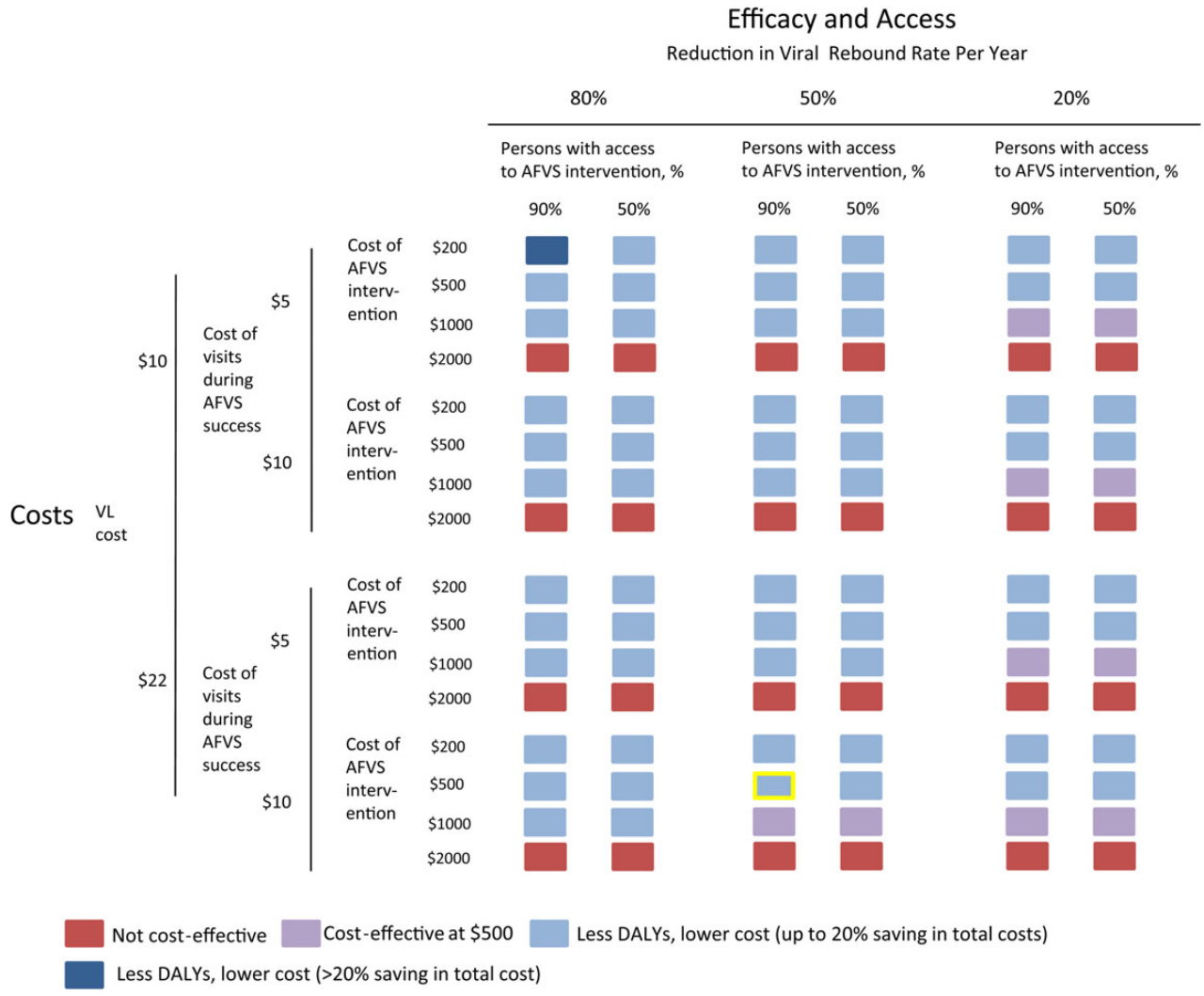

Figure 2. Results of multiway sensitivity analysis showing the effects of (1) efficacy and access of the antiretroviral therapy (ART)–free viral suppression (AFVS) intervention and (2) unit costs, on cost-effectiveness and level of cost saving. In the context of the base case, highlighted—90% of persons with access, 50% reduction in viral rebound rate per year, $22 for cost of viral load (VL), $10 for cost of visits during AFVS—the threshold cost of the AFVS intervention to be cost-effective was $1400, and the threshold to be cost saving was $975. Abbreviation: DALYs, disability-adjusted life years.

key determinants of the cost-effectiveness/impact of an AFVS intervention are the efficacy of the intervention (as defined by the rate of rebound over time) and the cost of the intervention. With the efficacy assumed in our base case, the AFVS intervention would need to cost <$1400 to be cost-effective.

The predicted benefits of an AFVS intervention depend on our predicted outcomes of ART. It is difficult to be certain about long-term outcomes of ART when potent regimens have been in use for <20 years, and for little more than 12 years in southern Africa. However, data on levels of viral suppression from sub-Saharan Africa indicate that therapy is highly effective [29, 40–43]. Long-term rates of virologic rebound in high-income settings have shown low and decreasing rates of viral rebound over time [28, 44]. Our sensitivity analyses suggest that if our model proves to be overly optimistic regarding ART efficacy—which is plausible given experiences in high-income countries—then more expensive AFVS interventions would become cost-effective and cost saving.

The costs associated with adopting the AFVS intervention are highest soon after introduction owing to the cost of the intervention itself and the increased intensity of viral load monitoring required in the initial period after the interruption. Without such frequent monitoring—3 monthly for 5 years—a significant proportion of persons could experience a sustained period of high-level viremia (higher than in those with viral breakthrough during ART). Over the longer term within our 20-year time horizon (to 2042) the AFVS intervention is associated with lower costs than continued ART.

The intention of this evaluation is to provide a source of guidance as research into potential AFVS interventions moves forward. The potential impact of an HIV vaccine has been evaluated in such a way previously [23, 45]. In addition, modeling and cost-effectiveness analyses have been used to identify the attributes of different types of cure approaches required to be cost-effective [46]. Specific cure strategies that were considered included gene therapy, chemotherapy, and stem cell transplantation. There are many similarities in the approach used with our own, with the use of individual-based simulation models that consider possible relapse rates and the consequences. The main differences concern our focus on sub-Saharan Africa rather than high-income settings, with substantial implications for the cost of cure regimens that might be cost-effective, and our inclusion via a dynamic transmission model of effects on HIV incidence.

In building our model of the AFVS intervention, we have not explicitly distinguished between an intervention that results in HIV eradication and one that results in sustained immune control of HIV. In the latter situation, the advantages might be that viral rebound, if it occurs, would be less dramatic, and that there may be protection from superinfection. A potential disadvantage is that, owing to the presence of low levels of virus, immune activation may persist, with less restoration of health. A potential additional benefit of an AFVS intervention that we did not include is that the availability of a cure may give an added impetus to ART programs and lead to higher levels of HIV testing and greater engagement with, and adherence to, ART with the prospect of access to the intervention.

One limitation of our work is that we naturally have had to make a number of assumptions. The success of prevention efforts and future HIV incidence are uncertain, although the impact of the AFVS intervention is not highly sensitive to these factors. The greatest uncertainties concerning this impact relate to the properties of the intervention and, to a lesser extent, the future effects of ART. In addition, we considered a time scale of 20 years, and the impact of the intervention would be expected to become greater with time, after a large initial investment. In addition, we assumed that third-line regimens are not available when in fact small numbers in Zimbabwe are using third-line regimens. We also assumed that preexposure prophylaxis would not be available, when it is likely to be used in future to some extent.

In conclusion, a new AFVS intervention has the potential to avert DALYs and result in substantial cost savings in HIV care. However, the intervention will need to meet a stringent set of specifications for this to be the case. The cure field can use models such as our to better define its product development and delivery system imperatives.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Author contributions. All authors contributed to defining the analysis concept and design, providing critical input to the conduct of the modeling analysis, and writing the manuscript. A. N. P., V. C., and F. N. developed the model and conducted the modeling analysis.

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