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Identifying key drivers of the impact of an HIV cure intervention in sub-Saharan Africa

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Abstract (200 words)

Background: The properties required of an intervention that results in eradication or control of HIV in absence of antiretroviral therapy (ART-free viral suppression) to make it cost-effective in low income settings are unknown.

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

Results: An ART-free viral suppression intervention with these properties would result in over 0.53 million disability-adjusted-life-years averted over 2022-2042, with a reduction in HIV programme 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.

Conclusion: Interventions aimed at curing HIV 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.

Introduction

Research is on-going into developing an intervention which would allow HIV positive individuals to have prolonged, and perhaps permanent, viral suppression in the absence of therapy ("remission", "cure"). We refer to this as antiretroviral therapy-free viral suppression (1-8). The implications of this research for sub-Saharan Africa, where most people 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 in order for it to be cost effective, or cost saving in low income, high HIV prevalence settings (i.e. a "target product profile") is important in order to focus research, clinical development and delivery approaches. Here, we sought to identify some basic product and delivery attributes within a framework of a global policy agenda. We address 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)? Secondly, 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 generalised HIV epidemic with on-going ART roll-out 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 previously described (20-23; and see Supplementary Material). Each simulation run generates time-updated longitudinal "data" over time for a population of people from 1989 such that the overall characteristics of the population in terms of age, gender, sexual risk behaviour and HIV status resembles that of the entire adult population of Zimbabwe (HIV positive and negative). Transmission of HIV is modelled, with the HIV status of each (condomless sex) partner being sampled, along with viral load status of HIV positive partners. For people who have become infected with HIV the variables for which longitudinal data are simulated include viral load, CD4 count, presence of resistance mutations, whether they have tested HIV positive, whether they are linked to care, whether they are maintained in care and on treatment, and occurrence of AIDS and death.

Evaluation of the impact of an ART-free viral suppression 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 composed of efavirenz/lamivudine/tenofovir and the second line regimen ritonavir-boosted atazanavir/zidovudine/lamivudine. It is assumed that no third line will be available. Table 1 presents the modelled 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 count changes, the rate of interruption of ART and of ART toxicity, as detailed elsewhere (Supplementary Material; 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 has been the case in the last

five years and that the policy will be for ART initiation in people with CD4 count <500 cells/mm^3 and option B+ for pregnant women from 2015. Viral load monitoring of people on ART is assumed to start from 2015 onwards. We also assume a modest increase in levels of condomless sex such that HIV incidence is projected to decline only modestly (Figure 1). We assume continuation of trends in male circumcision uptake and no introduction of pre-exposure prophylaxis.

ART-Free Viral Suppression Intervention

We envisaged an intervention that would induce ART-free viral suppression 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 the intervention is introduced in 2022 and that 90% of people in the country would have access to the intervention should they fulfil the eligibility criteria (50% in sensitivity analysis, perhaps more realistic if the intervention requires intra-venous administration). We assume that the eligibility criteria for the intervention is an undetectable viral load for at least 6 months and a CD4 cell count over 500 cells/mm^3. We consider that a cure intervention would be most likely to be started in people in whom ART had initially been used in order to reduce replicating virus. We assume that the ART-free viral suppression intervention would be administered for six months (while ART is continued).

We assume that 95% of those given the ART-free viral suppression intervention will be adjudged 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 (e.g. 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 x $0.5^{0.25}$; this equates to ~ 8% of people having viral rebound by 5 years after interruption of ART). Viral load and CD4+ T cell count dynamics during ART-free viral suppression failure were assumed to be comparable to that of an ART interruption. During periods of ART-free viral suppression, we assume that the CD4 count will continue to improve, as is the case with continued viral suppression on ART. We also assume that CD4 count- and age-specific morbidity and mortality will be no different to that in people on ART with viral suppression; i.e. including that there remains some residual excess risk over and above that in the uninfected population (1.3-fold 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 people on ART with viral suppression and 1.0-fold for those with ART-free viral suppression.

We assume that individuals who have received the ART-free viral suppression 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 people on ART). This is to try to ensure rapid identification of viral rebound if it occurs. We further assume that individuals with ongoing ART-free viral suppression are susceptible to super-infection, which will lead to viral rebound, while people on ART are assumed to not have risk of super-infection, due to the protective effects of ART.

Consequences of disengaging from care are different for people on ART and those with ART-free viral suppression. For those on ART, adherence to regular care / drug pick-up is essential for continued viral suppression. In contrast, for those who have successfully

achieved ART-free viral suppression, disengagement from care does not have negative consequences unless and until viral load rebound occurs

Those on ART with viral rebound will be eligible to be switched to second line - the rate of switch in such circumstances is 20% per 3 months once the above failure criteria are met. People are assumed to be given a maximum of one round of the ART-free viral suppression intervention.

Main Outcomes and Economic analysis

The time perspective of the analysis was 20 years (2022-2042). The main outcome is disability adjusted life years (DALYs) for individuals between ages of 15 and 65 years. The DALY is a measure of overall disease burden. A person incurs 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 under age 65 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, so that effects of transmission are accounted for.

A one-off cost of the ART-free viral suppression intervention of $500 ($200 and $2000 in sensitivity analyses) is assumed (including cost of viral load testing in the time before, and the first few weeks after, ART interruption). The cost of clinic visits during ART-free viral suppression success is assumed to be $10 per 3 months ($5 in a sensitivity analysis), compared with $20 for people on ART (33), the cost assumed lower as the person is not on ART. The current annual cost (including supply chain) of the first-line regimen is assumed to

be $144 per person per year, and the second-line regimen is assumed to cost $312 per person per year (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 that there is no increased mortality risk. A weight of 0.25 is approximately that estimated for severe diarrhoea, acute low back pain, or acute gout, for example (35). A disability weight due to living with diagnosed HIV is taken as 0.1 (36). This is removed in those with ongoing ART-free viral suppression 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 if resources were 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 over half of gross domestic product per capita (39). DALYS, life years and costs were discounted from 2014 values at 3% per annum. The ART-free viral suppression 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 below $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 count 500 cells/mm^3 and with adoption of option B+ for pregnant women, the proportion of people with HIV who are diagnosed, and the number of people on ART is projected to increase. As a result of these assumptions, approximately 300,000 individuals between age of 15 and 65 are projected to be both eligible for, and have access to, the ART-free viral suppression intervention in 2022 (26% of the entire HIV-positive adult population in the country at that time).

The proportion of people who will receive the ART-free viral suppression intervention is expected to rise to 65% in 2042 (Supplementary Figure 2(a)). The number of people with on-going ART-free viral suppression (Supplementary Figure 2 (b)) is projected to approach a maximum of 550,000 by the early 2030s. The incidence of ART-free viral suppression failure (viral rebound) is highest soon after the AVFS program is launched as large numbers of people will access the therapy when it first becomes available and most failures occur early (Supplementary Figure 2 (c)).

HIV incidence is projected to decline with or without the ART-free viral suppression intervention (due to enduring effects of earlier reductions in condomless sex in the mid 1990s and effects of viral suppression with ART), but is projected to be somewhat lower with the ART-free viral suppression intervention (Supplementary Figure 2 (d)). Likewise, prevalence of HIV (where people with on-going ART-free viral suppression success remain classified as being HIV positive), is projected to decline regardless of introduction of the ART-free viral

suppression intervention, but slightly more rapidly with the ART-free viral suppression intervention (Supplementary Figure 2 (e)). The number on ART will decline to below 700,000 by 2042 without the ART-free viral suppression intervention, and to be below 400,000 if the ART-free viral suppression intervention is introduced (Supplementary Figure 2 (f)). The overall proportion of people with HIV who have viral load unsuppressed (> 500 copies/mL) is projected to decline only slowly from the level of 40% in 2022 without the ART-free viral suppression intervention, but to decline to close to 25% with introduction of the ART-free viral suppression intervention (Supplementary Figure 2 (g)). The death rate in people with HIV is projected to be lower with the ART-free viral suppression intervention by around 0.5 per 100 person years (8.4% lower; Supplementary Figure 2 (h)). DALYs (discounted) will be slightly lower with the ART-free viral suppression intervention (Supplementary Figure 2 (i)). Costs are higher with the ART-free viral suppression intervention in the initial few years of introduction due to the costs of the ART-free viral suppression intervention but thereafter costs are lower, due largely to less people being on ART (Supplementary Figure 2 (j)). Further outputs are shown in Supplementary Figure 2(k) onwards.

With regard to projected costs, the main differences between the scenario with and without an ART-free viral suppression intervention are the cost of ART, the cost of the ART-free viral suppression intervention, the cost of clinic visits (less expensive in people with ART-free viral suppression), and the cost of viral load tests (since these are done more frequently in people with ART-free viral suppression) (Figure 1). The ART-free viral suppression 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 age 15-65 (Table

3). The ART-free viral suppression intervention also results in a reduction in costs of $298m (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 ART-free viral suppression intervention (Supplementary Figure 3). Assumptions about the degree to which ART is expected to be durably successful affect the magnitude of benefit of the ART-free viral suppression intervention. In particular, when we assume a higher rate of interruption of ART (such that only 63% of ART experienced people have viral load < 500 cps/mL, compared with 73% in the base case), the intervention benefit is greater. The benefit of the ART-free viral suppression intervention is also greater if we assume that the rate ratio compared with the HIV negative population for non-AIDS mortality in people in people with ART-free viral suppression success is 1.0, but higher (at 1.3 fold or 1.7 fold) for people with viral suppression on ART. If the disability weight from ART toxicity is assumed to be 0.15 rather than 0.05 then the impact of the ART-free viral suppression intervention is again greater.

Figure 2 presents the cost-effectiveness of the ART-free viral suppression intervention according to variation in combinations of key uncertain parameters of ART-free viral suppression efficacy and access, and cost parameters. The most strongly influential of these factors for cost-effectiveness is the cost of the ART-free viral suppression 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 ART-free viral suppression intervention to be cost-effective is $1400, and the threshold to be cost-saving is $975. If the ART-free viral suppression intervention efficacy is lower, such that the % reduction in viral rebound rate / year is instead 20%, then the threshold cost of the

ART-free viral suppression intervention to be cost-effective is $1000 and the threshold cost to be cost saving is $700.

Discussion

In this modelling and economic evaluation we have assessed what properties an intervention aimed at HIV "cure" should have in order for it to represent a cost effective option in low resource settings. The key determinants of the cost effectiveness / impact of an AVFS 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 ART-free viral suppression intervention would need to cost below $1400 in order to be cost-effective.

The predicted benefits of an ART-free viral suppression 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 less than 20 years, and for little over 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 then more expensive ART-free viral suppression interventions would become cost-effective and cost-saving.

The costs associated with adopting the ART-free viral suppression intervention are highest soon after introduction due 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 people could

experience a sustained period of high level viraemia (higher than that in people with viral breakthrough on ART). Over the longer term within our 20 year time horizon (to 2042) the ART-free viral suppression intervention is associated with lower costs than continued ART.

The intention of this evaluation is to provide one source of guidance as research into potential ART-free viral suppression interventions moves forward. The potential impact of an HIV vaccine has been evaluated in such a way previously (23, 45). In addition, modelling 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 which 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 ART-free viral suppression 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, advantages might be that viral rebound, if it occurs, would be less dramatic, and that there may be protection from super-infection. A theoretical potential disadvantage is that due to presence of low levels of virus there may remain persistent immune activation and less restoration of health.

A potential additional benefit of an ART-free viral suppression intervention that we did not include is that the availability of a "cure" may give an added impetus to ART programmes and lead to higher levels of HIV testing and greater engagement with, and adherence to, ART if there is the prospect of access to the intervention.

Our work has the limitation 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 ART-free viral suppression intervention is not highly sensitive to these factors. The greatest uncertainties of the impact of the ART-free viral suppression intervention relate to the properties of that 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 of people in Zimbabwe are on third line regimens. We also assumed that pre-exposure prophylaxis would not be available when it is likely to be used in future to some extent.

In conclusion, a new ART-free viral suppression 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 in order for this to be the case. The cure field can utilize models such as this to better define its product development and delivery system imperatives.

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Author Contributions

All authors contributed to defining the analysis concept and design, providing critical input to the conduct of the modelling analysis, and writing the manuscript. AP, VC and FN developed the model and conducted the modelling analysis.

Conflicts of Interests

Dr. Phillips reports grants from BMGF, during the conduct of the study; personal fees from Gilead Sciences, personal fees from Abbvie, personal fees from GSK Biologicals, personal fees from Ashfield Communications, outside the submitted work. Dr. Hallett reports grants from BMGF, World Bank, UNAIDS, Rush Foundation, Wellcome Trust, personal fees from BMGF, New York University, WHO, GFATM, outside the submitted work.

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Table 1. Illustration of the modelled effect of ART. Model outputs of status in 2025 and 2035 for people starting ART in 2015. These outputs reflect model assumptions regarding multiple aspects, including adherence patterns, resistance acquisition, effect of adherence and resistance on virologic outcome and CD4 count changes, the rate of interruption of ART and of ART toxicity*.

Outcome	**Model outputs of status at 10 and 20 years from start of ART for people starting ART in 2015**	
	10 years from start of ART (i.e. in 2025)	**20 years from start of ART (i.e. in 2035)**
On ART with viral load < 1000 copies/mL	53%	31%
On ART with viral load > 1000 copies/mL	6%	3%
Alive but off ART	9%	5%
Dead from HIV disease	20%	40%
Of those alive on ART, percentage experiencing an ART toxicity	37%	34%
Of those alive on ART, percentage on second-line ART	24%	37%

Of those alive on ART, percentage with NNRTI drug resistance	44%	56%
Of those alive on ART, percentage with resistance to NNRTI, NRTI and PI classes	1%	2%

* Full details of modelling of effect of ART are given in Supplementary Material. Also see supplementary material for details and comparison of outputs for adherence, virologic outcome, NNRTI resistance, ART discontinuation (20-29) See also references 20-23 for additional details.

Table 2. Characteristics of the simulated population of Zimbabwe in 2014 and 2020

Output	2014	2020	Observed data
Population size age 15-65	7,971,000	8,946,000	8,000,000[&]
Number tested for HIV (per 3 months)	687,000	882,000	2,274,328 age 15-49 tested in 2013*
Proportion of men circumcised (age 15-65)	0.27	0.46	0.26 in men age 15-29 in 2014[^]
Incidence of HIV (per 100 person years) age 15-65	0.99	0.61	0.98 in 2013*
Prevalence of HIV age 15-49	0.14	0.11	0.15 in 2011 DHS**
Number living with HIV	1,167,000	1,124,000	
Of people with HIV, proportion diagnosed	0.84	0.91	
Number on ART (age 15-65)	678,000	801,000	~700,000 on 1st Jan 2015***
Of people diagnosed with HIV, proportion ever started ART	0.75	0.87	
Of people with HIV, proportion	0.58	0.78	

on ART			
Death rate (per 100 person years) in whole adult population age 15-65	1.81	1.57	1.15 age 15-49**
Death rate (per 100 person years) in people with HIV age 15-65	5.45	4.54	
Death rate (per 100 person years) in people on ART age 15-65	4.13	3.20	
Of people on ART, proportion with VL below 500 copies/mL	0.81	0.84	0.78 +
Of people who ever started ART, proportion who have started 2nd line	0.05	0.19	< 0.02***
Of people with HIV, proportion with VL above 500 copies/mL	0.52	0.39	
Of people who ever started ART, proportion who have failed first line	0.13	0.24	

& CIA World Factbook 2015 (https://www.cia.gov/library/publications/the-world-factbook/geos/zi.html).

* UNAIDS. Global AIDS Response Country Progress Report. Zimbabwe 2014. ^ Data from PSI, Zimbabwe (personal communication). ** Zimbabwe National Statistics Agency (ZIMSTAT) and ICF International. 2012. *Zimbabwe Demographic and Health Survey 2010-*

11. Calverton, Maryland: ZIMSTAT and ICF International Inc. *** personal communication J Murungu MoHCC. + baseline results SAPPH-IRe trial;

Table 3. Discounted DALYs and costs over 20 years (2022-2042) with and without ART-free viral suppression intervention. Base case.

	ART-free viral suppression intervention	**No ART-free viral suppression intervention**
DALYs	46,610,496	47,150,234
DALYs averted compared with no ART-free viral suppression intervention	539,738	----
Costs (in $m)*	$3,139	$3,437
Increment in costs (in $m) compared with no ART-free viral suppression intervention	-$298	----

* 8.7% reduction in costs with ART-free viral suppression intervention

Figure Legends

Figure 1. Overall programme costs in ($m over 20 years from 2022-2042) according to whether the
ART-free viral suppression (AFVS) intervention is introduced or not (discounted at 3% per annum from 2015)

Figure 2. Results of multi-way sensitivity analysis showing the effects of (i) efficacy and access of the ART-free viral suppression (AFVS) intervention and (ii) unit costs, on the cost effectiveness and level of cost saving. In the context of the base case, highlighted, (% of people with access = 90%, % reduction in viral rebound rate / year = 50%, cost of viral load $22, cost of visits during ART-free viral suppression success $10), the threshold cost of the ART-free viral suppression intervention to be cost-effective = $1400, and the threshold to be cost-saving = $975.

Overall programme costs in ($m over 20 years from 2022-2042) according to whether the ART-free viral suppression (AFVS) intervention is introduced or not (discounted at 3% per annu