Evaluating Strategies to Improve HIV Care Outcomes in Kenya

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# Abstract (300 words)

## Background:

With expanded access to anti-retroviral therapy (ART) in sub-Saharan Africa, life expectancy has increased, yet life-years are still lost to AIDS. We aimed to examine the state of a current HIV care programme in Kenya and assess the potential for interventions to improve the impact of ART programmes on population health.

## Methods & Findings:

We constructed an individual-based mathematical model to describe the HIV epidemic and the experiences of care among HIV-infected adults in Kenya. We calibrated the model to a longitudinal dataset from The Academic Model for Providing Access To Healthcare (AMPATH) describing the routes into care, losses and clinical outcomes. Between 2010 and 2030, we estimate that the majority of AIDS-related deaths in this population would be among persons that have been diagnosed with HIV but never initiated treatment (57%). Other predicted drivers of mortality are late initiation (9%) and disengagement with care following initiation of ART (12%). We used the model to simulate the cost and impact of a range of interventions, based on earlier trial results, to improve the cascade of care individually and in combination. We find that no individual intervention is expected to provide a large benefit, because any single intervention is confounded by other weaknesses in the cascade. However, two approaches can be recommended: a combination of interventions (including improved linkage and adherence to treatment together with pre-ART and ART outreach strategies) would generate a large impact (4.45M DALYs averted between 2010 and 2030) cost-effectively ($360 per DALY averted); or a shift to providing treatment to all HIV-infected persons immediately upon presentation (3.62M DALYs averted between 2010 and 2030, and $453 per DALY averted). Either strategy would generate health more cost-effectively than a expansion of testing and treatment without improvements in the cascade (4.05m DALYs averted at $905 per DALY averted).

## Conclusions:

Our results suggest limited linkage from testing is the major driver of mortality in a programme in Kenya and greater health benefits could be generated by strengthening each part of the cascade, or by switching to treating HIV-infected persons immediately when they present to care. In contrast, an expansion of treatment programmes, without such improvements would not maximize health benefits in a resource-limited setting. International guidance on ART should reflect these alternate routes to programme strengthening, recognize outreach as an integral part of treatment intervention, and encourage country programmes to evaluate the costs and impact of ART expansion in addition to the clinical benefits of earlier initiation.

# Introduction

The major success story in the response to the HIV pandemic has been the development and provision of anti-retroviral therapy{UNAIDS:2014ta}. With timely diagnosis, treatment can increase life-expectancy such that it approaches that of an HIV-negative individual{Nakagawa:2013cv}. Consequently, adult life expectancy has increased by more than 11 years in South Africa as a direct result of ART becoming accessible{Bor:2013er}. However, in the worst affected countries, there are still estimated to be hundreds of thousands of AIDS-related deaths each year{UNAIDS:2014ta}. Furthermore, studies in Uganda and Rwanda have revealed that the life expectancy of men and women initiating ART still falls below that of the general population, indicating life-years are still being lost to HIV{Nsanzimana:2015dm,Mills:2011gx}. In this era of widespread ART availability, why are such large health losses continuing and what can be done to improve the population health generated by ART programmes?

The reasons for continued health losses to HIV are not well understood but attention has recently focused on the ‘care cascade’{McNairy:2012dg}. This describes the series of events and consultations through which HIV-infected individuals must pass in order to benefit fully from ART, beginning with HIV testing, and ending with regular monitoring of patients in a state of sustained viral suppression. In 2011, Fox and Rosen highlighted how fewer patients reach each successive stage of HIV care in sub-Saharan Africa{Rosen:2011ii}, and this was followed by reports detailing the care cascade as it appears to operate in different countries{Nachega:2014ks, Nosyk:2013em, Kilmarx:2013iy, Fox:2014ch}. However, many of these studies have been limited by not having the opportunity to follow the same patients through all stages of the cascade, as they typically focus on the subset of the population that presents to a clinic, and are therefore blinded to the outcomes of patients that never engage or disengage from care.

In recent years there has been a proliferation in innovative approaches to improving the care cascade{Govindasamy:2014fa, Barnighausen:2011cb}. These variously aim to improve testing, linkage to care, retention in pre-ART care, retention in post-ART care and rates of viral suppression. Many of these strategies have been subject to trial and have met with remarkable success. For example, in South Africa van Rooyen *et al.* trialled a home-based counselling and testing (HBCT) intervention achieving 91% coverage of the community, with 96% of newly diagnosed individuals linking to care within six months after receiving point-of-care CD4 testing and follow-up visits{vanRooyen:2013gy}. In another trial, Jani *et al.* were able to reduce pre-ART loss to follow up in Mozambique from 64% to 33% through the use of a POC CD4 intervention{Jani:2011eb}. Additionally, Long *et al.* were able to reduce loss to follow up and annual care costs in South Africa through a decentralising intervention that involved transitioning stable patients on ART from a hospital to a primary health care facility{Long:2011cx}. However, other strategies have been less successful, with the results of an HBCT trial at another AMPATH site in Kenya reporting that only 15% of newly diagnosed individuals linked to care over a median of 3.4 years since diagnosis{Genberg:2015cd}. Furthermore, these trials fail to capture the population-level health gains, such as long-term or knock-on effects to persons not directly reached with an intervention. Additionally, the combined impact of interventions targeting different areas of the cascade has not been examined in trials to date.

While it is increasingly recognised that strengthening of the cascade is required, there is also a continued push for the rapid expansion of treatment, including expanding eligibility criteria to potentially all HIV-infected persons, and to increase active outreach to populations for testing (i.e. through a Universal Test and Treat strategy)

{Eaton:2013bv,UNAIDS:2014vh}. This can be thought of as an alternative, transformational, intervention in the care cascade. In hypothetical idealised programmes, there are persuasive arguments in favour of such an approach

{Eaton:2013bv}, but the extent to which this is the right approach given the apparent fragility of some current health systems, has been unclear, and may also be a source of concern with respect to the equality of health benefits to patients.

As a result, programme managers facing the question of understanding the drivers of AIDS-related mortality in the communities they serve, are having to decide which of the potential ‘care cascade’ interventions should be prioritised, with little data to guide them in making decisions about how to generate the greatest gains in population health given the available resources. However, mathematical models combined with longitudinal data from real programmes offer a means to draw conclusions about the way in which programmes should develop. The AMPATH programme furnishes unique data on the care cascade in western Kenya including information on persons prior to testing and disengaged from care, through an integrated household-based testing intervention with active follow-up. We have used these data to calibrate an individual-based mathematical model that represents the HIV epidemic in western Kenya and the experience of care for HIV-infected patients. With this, we produce the first estimates of the drivers of AIDS-related mortality in a population benefitting from a mature ART-programme. We are then able to use the model to estimate the cost and impact of potential interventions, in isolation and in combination, examining the effects on patient health and downstream care benefits simultaneously. In this way, we are able to arrive at broad recommendations about how programme managers can modify their programmes to maximise health cost-effectively.

# Methods

*Overview*

We constructed an individual-based micro-simulation model representing the HIV epidemic in western Kenya and capturing the care experience of individuals as they progress through an ART programme. We reviewed literature on how interventions can be used to improve elements of the care cascade and simulated their effects in the model.

The model is briefly described below in three sections: (i) Epidemic and natural history assumptions; (ii) Representation of the care cascade at baseline; and (iii) Interventions on the care cascade. Further details are presented in Text S1.

1. ***Epidemic and Natural History Assumptions***

The micro-simulation model represents births, ageing and deaths among the population of Kenya, using data from the United Nations Population Division{WorldPopulationPro:vq}. The risk of HIV incidence, for persons of a particular age and sex at a particular time, is equal to the estimates published by UNAIDS for the years 1980-2001. We used national level HIV estimates to characterise the population in western Kenya as long-term district-level incidence estimates are unavailable and also we aimed at producing broad recommendations based on the functioning of a mature ART programme in Kenya, not specifically western Kenya. For the years following 2001, incidence in the model is re-calculated to reflect the growing number of persons on ART and to enable there to be feedback from a successful ART programme reducing new HIV infections.

Following infection, disease progression is modelled by an individual falling to states of lower CD4 cell count category (>500, 350-500, 200-350 and <200 cells/µl) and to states of greater disease severity (WHO stages I, II, III and IV). An individual’s CD4 cell count and disease state are both tracked as they have independent predictive effects on the risk of mortality, and the latter is also assumed to predict the propensity to seek care. Rates of transitioning through these stages were inferred through fitting the model to all available surveillance data on HIV/AIDS natural history.

When an individual on ART has a suppressed viral load, they can transition to a higher CD4 cell count and lower disease severity category. Transition rates are informed through fitting the model to surveillance data on CD4 reconstitution rates{Lawn:2006ht}, together with mortality rates stratified by CD4 count and WHO stage from the IeDEA Southern Africa initiative{May:2010ee}. If an individual ceases ART, following a period of successful viral suppression, they will again progress to lower CD4 cell counts and higher disease states.

Model outputs were then compared to UNAIDS national estimates of HIV prevalence, incidence, AIDS-related deaths and ART coverage. Further comparisons were also made to national and provincial estimates of HIV prevalence from the Kenya AIDS Indicator Survey (KAIS) 2007 and 2012 rounds before comparing model output to HIV prevalence estimates from AMPATH. Further details presented in Text S1.

1. ***Representation of the Care Cascade at Baseline***

The model describes the pathway through care for each HIV-infected individual (Figure 1). Care begins with the identification of HIV-positive individuals through HIV-testing. This can be through seeking care voluntarily at a voluntary counselling and testing clinic (VCT), or in a healthcare setting through provider-initiated counselling and testing (PICT). Alternatively, as one of the intervention scenarios, the patient may be sought and diagnosed at home by a home-based counselling and testing team (HBCT) (see below). Diagnosis is followed by linkage to care, whereby an individual is seen by a clinician in an HIV clinic. Patients presenting with WHO Stage III/IV symptoms can be fast-tracked to initiate treatment immediately. Otherwise, a blood sample is taken for a CD4 test in order to determine their eligibility for ART. Patients then return after a month to receive their CD4 test results and learn of their eligibility for treatment. If a patient is not immediately eligible for treatment, they return in one year for a follow-up CD4 test and are held in pre-ART care until they become eligible. Once eligible, patients initiate ART, and if highly adherent will become virally suppressed. At each point, patients can disengage and become lost from care, but have the opportunity to re-engage at a subsequent date depending upon previous health care experience and current health state.

**Figure 1. Flow diagram representing the operational steps involved in navigating an ART-programme.** Blue arrows denote ‘linkage’ step that is successful upon a patient being seen by a clinician where blood is taken for a CD4-test. Dashed arrow denotes ART re-initiation after loss from ART care (does not occur at baseline).



The model was parameterised using data from AMPATH. The AMPATH Medical Record System (AMRS) has been collecting individual-level data on the AMPATH HIV control system since 2007{Einterz:2007js, Tierney:2007th}. Service delivery occurs through public sector hospitals and 65 health facilities run by Kenya’s Ministry of Health{Wachira:2013dc}. Building on well established VCT and PICT programmes, the use of HBCT was first trialled in eight catchment areas in 2007 before becoming a permanent AMPATH-wide intervention in 2010{Wachira:2013dc}.

In this setting of Port Victoria, an AMPATH facility opened in 2006 providing care through VCT and PICT. In the area of Bunyala, there have additionally been multiple rounds of household-based testing campaigns since 2010, the first of which achieved >85% coverage of the community (Personal communication from Paula). We used these data to fully characterize the care cascade through the use of data as input parameters to the model, or otherwise adjusted parameters that were not directly observed in order to induce an agreement between the model and data (Table 1). The baseline scenario of the analysis represents the programme just prior to the implementation of HBCT in this population.

We constructed two scenarios for the baseline simulation. The first represented the best interpretation of the data where patients naturally sought care as a function of decreasing health and previous care experience. As patients progressed further through pre-ART care and became progressively sicker, their propensity to seek care increased. The second scenario, whilst consistent with most data, did not include this relationship between care seeking behaviour, decreasing health and care experience. This relationship has previously been noted as a potential modifier on the effect of cascade interventions, and quantification of the magnitude of the effect is provided by the comparison of the estimated effects of interventions with respect to each of these two baselines.

ART-programme costs at baseline were estimated from the perspective of a health care provider, based on the recent CHAI MATCH study of ART facilities, and assumed to be comprised of the cost of ART care, the cost of pre-ART clinic visits and the cost of CD4 lab-based tests{Tagar:GTMxY-pi}.

1. ***Interventions on the Care Cascade***

Interventions on the care cascade can be divided into those that aim to increase testing, linkage and retention in pre-ART care, or retention and suppression for patients on ART. We reviewed the literature to identify realistic assumptions for the efficacy and cost of representative interventions in each of these categories (Table 2). An enhanced version of each intervention was also investigated to determine the maximum possible impact of a single intervention (results in Text S1).

To assess the impact of individual interventions, each intervention was implemented in turn from 2010 onwards and the effect on patient outcomes compared to the baseline scenario. The impact of the programme is quantified in terms of DALYs averted, additional cost and HIV-related deaths averted, with respect to a baseline ‘status quo’ programme similar in structure to AMPATH before the launch of household-based testing.

To assess the cost-effectiveness of interventions, the cost per DALY averted was compared the gross domestic product (GDP) per capita for Kenya in 2013 ($1,242){Bank:ypJvNfII}. An intervention is deemed cost-effective if a DALY can be bought for less than half the GDP per capita (cite Paul Revill?).

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| **Description** | | **Route of entry to care** | **AMPATH Data** | | | **Model** | | |
| Input Parameters | Proportion of individuals who received initial CD4-test returning for test results within one month | *HCT* | 62% | | | 62% | | |
| *VCT* | 53% | | | 53% | | |
| *PICT* | 54% | | | 54% | | |
| Proportion that ever return for secondary CD4 tests | *HCT* | 43% | | | 43% | | |
| *VCT* | 31% | | | 31% | | |
| *PICT* | 31% | | | 31% | | |
| Calibration Points | Proportion of individuals that ever enter care | *Date* | *2007 - 2010* | *2010 - 2011* | *2011 - 2014* | *2007 - 2010* | *2010 - 2011* | *2011 - 2014* |
| *HCT* | - | 7% | 60% | - | 38% | 57% |
| *VCT* | 66% | 47% | 20% | 61% | 33% | 24% |
| *PICT* | 34% | 46% | 20% | 39% | 28% | 19% |
| Proportion in each CD4 category at ART initiation | *CD4 >500* | 9% | 14% | 19% | 0% | 0% | 0% |
| *CD4 350-500* | 7% | 8% | 18% | 1% | 2% | 1% |
| *CD4 200-350* | 18% | 21% | 41% | 3% | 2% | 32% |
| *CD4 <200* | 66% | 57% | 22% | 96% | 96% | 67% |
| On 1st January 2010 | *Proportion of PLWHIV diagnosed* | 62% | | | 62% | | |
| *Proportion diagnosed through VCT* | 66% | | | 66% | | |
| *Proportion diagnosed through PICT* | 33% | | | 34% | | |

**Table 1. Summary of agreement between AMPATH data and the model.** AMPATH data was separated into three discrete time periods: 2007 to 2010 marking the period of time prior to household-based testing where individuals could only seek care through VCT or PICT, 2010 to 2011 in which HBCT was rolled out in Port Victoria and 2011 to 2014 when HBCT was fully implemented and treatment eligibility guidelines had been updated to <350 cells/µl or WHO Stage III/IV. On 1st January 2010 denotes the cross-sectional state of care in Port Victoria at the beginning of 2010.

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| **Aspect of care to be addressed** | **Intervention type** | **Intervention** | **Assumptions** | **Cost**  **(2013 USD)** |
| Individuals are initially unaware of their HIV infection. At baseline, the mean time for an individual to test through VCT is 7.2 years. Additionally individuals may test through PICT, and the time to test varies depending on prior health care experience and symptoms: Asymptomatic and no previous care experience = 15.6 years. Asymptomatic and diagnosed = 11 years. Asymptomatic and aware of CD4 count = 5 years. Symptomatic = 1.5 years. | *Testing* | ***HBCT*** | Every four years, 90% coverage. 5% linked if had not previously been diagnosed, else 25%. | $18 per HBCT person tested ($8 home-visit [*Barnabas unpublished*] + $10 rapid HIV-test{Wright:2004jd}). |
| ***Enhanced VCT*** | The rate of HIV testing is 125% that of baseline. | $50 per person tested ($28 clinic visit{Tagar:GTMxY-pi} + $10 rapid HIV-test {Wright:2004jd} + $12 CD4 lab test{Tagar:GTMxY-pi}). |
| *Testing & Linkage* | ***HBCT (with POC)*** | Every four years, 90% coverage of population. POC CD4 reduces risk of not linked by 50%. | $60 per HBCT person tested ($8 home-visit [*Barnabas unpublished*] + $10 rapid HIV-test{Wright:2004jd} + $42 POC-CD4 test{Larson:2012dq}). |
| In some cases, individuals are not connecting to care following diagnosis in timely manner. At baseline, 60% of patients tested through VCT or PICT successfully link to care immediately. | *Linkage* | ***Facilitated Linkage*** | The risk of failure-to-link is reduced by 50%. | No additional costs applied. |
| ***VCT POC CD4*** | At VCT testing, a POC CD4 test is given to patients reducing the risk of not linking to 0%. | $80 per POC CD4 test ($28 clinic visit{Tagar:GTMxY-pi} + $10 rapid HIV-test {Wright:2004jd} + $42 POC-CD4 test{Larson:2012dq}). |
| Individuals that have linked to care can sometimes subsequently disengage prior to starting treatment. On average at baseline, for every CD4 test 56% of patients disengage from care before receiving their results. On the day of a CD4 test result appointment, 20% of patients do not attend and are also lost from care. After receiving the results of a CD4 test, on average 35% of patients fail to return for a subsequent CD4 test in a years time. | *Pre-ART Retention* | ***Pre-ART Outreach*** | In the middle of each year, 20% of tested individuals lost from care are returned. | $19.55 per patient sought{Rosen:2010ca}. |
| ***Improved Care*** | The risk of a patient missing an appointment is reduced by 50%. | No additional costs applied. |
| ***POC CD4*** | A POC CD4 test reduces loss from care between CD4 test and result by 100%, as results are available instantaneously. (The risk of loss to follow-up between appointments is unchanged). | $70 per POC CD4 test ($28 clinic visit{Tagar:GTMxY-pi} + $42 POC-CD4 test{Larson:2012dq}). |
| Individuals initiate ART but subsequently disengage from care. At baseline, 8% dropout in the first year of ART and 5% per year thereafter. | *On-ART Retention* | ***On-ART Outreach*** | In the middle of each year, 40% of patients who have initiated ART and been lost from care are returned. | $19.55 per patient sought{Rosen:2010ca}. |
| Some individuals on ART do not adhere sufficiently to fully benefit from effects of ART. | ***Adherence*** | At ART initiation, 87.5% of individuals adhere to ART and become virally suppressed. | $33.54 per person per year{Sarna:2008tb}. |
| Pre-ART care as a whole. | *Sweeping Changes* | ***Immediate ART*** | No pre-ART care, all individuals who enter care are treated immediately. | Only additional costs due to increased usage of ART. |
| ***Universal Test & Treat*** | Immediate ART & HBCT (every four years, 90% coverage. 5% linked if had not previously been diagnosed, else 25%) | $18 per HBCT person tested ($8 home-visit [*Barnabas unpublished*] + $10 rapid HIV-test{Wright:2004jd}). |

**Table 2. Summary of individual interventions designed to target various aspects of care.**

# Results

## Current Sources of Health Losses

We first projected the ‘status quo’ model to 2030 and analysed the status of care at the time of death for those expected to die of AIDS in the period 2010 to 2030 (Figure 2). The model finds that among all AIDS-related deaths, the majority (57%) would occur in individuals who were diagnosed with HIV but who did not ever start treatment (Figure 2, left). A further 19% of AIDS-related deaths would be among persons who never engaged with care prior to death, with the remainder among those who started ART.

Most data systems, however, do not benefit from such a holistic view of the population and instead are based solely upon data around those who attend a clinic at least once (Figure 2, right). In that case, 33% of all AIDS-related deaths would be not apparent and a major driver of deaths (not being diagnosed with HIV) would not feature among the leading causes of mortality in that population. Patients presenting with WHO Stage III/IV symptoms can be fast-tracked to initiate treatment immediately.

With 76% of AIDS deaths predicted to occur among those that never start treatment, this indicates that changes to programmes delivering ART may have greater scope to improve health than changes in the therapy and monitoring of patients on-ART. The nature of these potential changes to an ART programme was then investigated.

**Figure 2. Care experience of patients suffering HIV-related deaths between 2010 and 2030.** The community perspective, accounting for all HIV-related deaths (left). The clinic perspective, accounting for all HIV-related deaths among individuals who came into contact with the clinic at least once (right).



## The Impact of Cascade Interventions

We applied each of the 12 potential interventions in turn and assessed the impact on DALYs averted, compared to baseline, and the additional cost of care, compared to baseline, between 2010 and 2030 (Figure 3 and Table 3).

Broadly, the effects of most single interventions cluster together with relatively low impact and low cost. This is because there are weaknesses throughout the care cascade, so interventions acting at one point alone cannot have a large impact, as they are confounded by remaining weaknesses elsewhere.

The exception to this is HBCT, which attracts a high cost given its projected benefit. This is due to the assumption that only a small proportion of persons being diagnosed for the first time at HBCT will link to care without further intervention (5%), based on observations in AMPATH{Genberg:2015cd}. HBCT with POC CD4, by increasing linkage and reducing the time needed to determine patient eligibility for ART, accrues nearly twice as many DALYs averted for a small increase in costs.

The two interventions that effect large changes to the delivery of ART – Immediate ART and Universal Test and Treat (UTT) – both have much greater impact than any other intervention. Providing treatment to those presenting for care immediately is highly impactful because the model assumes that a large number of people would naturally present for care without additional outreach costs (as seems to occur in this population), and benefit is accrued by eliminating the potential for losses from pre-ART care. With a cost per DALY averted of $453, this intervention is cost-effective at the threshold of 50% GDP per capita ($621). The UTT intervention, by contrast, is much more costly as the outreach costs are estimated to be very large ($905 per DALY averted, not cost-effective); but this intervention is more impactful because the addition of an outreach intervention such as HBCT allows ART coverage in the population to reach higher levels.

In contrast to HBCT, enhancing VCT provides less benefit ($1,683 per DALY averted, Table 3) and this is due to the high level of VCT testing at baseline and the high cost associated with identifying an HIV-positive individual in the population. However, individuals testing through VCT appear to be more likely to link to care than those testing through HBCT without further intervention.

Providing POC CD4 to individuals testing through VCT improves linkage to care and informs persons immediately of their eligibility for treatment. Improving awareness of treatment eligiblity at the point of diagnosis averts downstream losses in pre-ART care and allows eligible patients to initiate treatment sooner. Preventing loss from pre-ART care appears more beneficial than returning patients lost from care, as evidenced by the improved care and pre-ART outreach interventions: the cost per DALY averted compared to baseline for improving care (reducing drop-out) is 26% lower than the pre-ART outreach intervention ($373 vs. $510, respectively).

Under an alternative baseline assumption that people will not naturally seek care naturally as their health deterioriates, the interventions generate greater impact (Text S1). The two exceptions to this are the ART outreach and adherence interventions that are restricted by the number of patients that ever initiate ART at baseline.

The impact of each individual intervention is moderately weakened if transmission benefits are removed from the model. Interventions are, on average, 20% less impactful and 8% more expensive without transmission benefits. Pre-ART outreach intervention has the largest reduction in impact (28%), while immediate ART has the largest increase in cost (25%). This indicates that while transmission benefits enhance interventions, the majority of health benefits are accrued from direct effects reducing losses from care as opposed to the indirect impact of reducing the potential for onward transmission of infection (Text S1).

## The Impact of Bundles of Interventions

An optimal combination of cascade interventions was found by simulating all possible combinations and selecting those that, at each budget level, provided the greatest increase in health. We imposed the additional constraint that, once an intervention had been included in the combination at one budget level, it cannot be removed at higher budget levels.

This finds that a combination of six interventions would be prioritised in this setting (Table 4). The identified interventions include: pre-ART outreach, linkage, VCT POC CD4, POC CD4, ART-outreach and adherence. Importantly, this combination of interventions includes elements that act on each part of the cascade. As the major driver of AIDS-related deaths in this setting was found to be among persons diagnosed but who not initiated treatment, interventions that increase linkage (including POC CD4) and retention in pre-ART attract most investment.

Collectively this combination of interventions has a larger impact on reducing AIDS-related mortality and averting DALYs than the UTT intervention (38% vs. 32% of baseline AIDS-related deaths, and 4.45m vs. 4.05m DALYs averted), but is estimated to cost only 39% as much ($353 vs. $905 ACER) and is therefore very cost-effective at the 50% GDP per capita threshold of $621. This combination of cascade interventions is a similar cost as the immediate ART intervention but is estimated to have a slightly greater impact ($1.57b vs. $1.64b, and 4.45m vs. 3.62m DALYs averted). The comparatively low cost and high impact of the combination cascade intervention is the result of a collection of interventions operating synergistically, whereas the UTT and immediate ART interventions operate with inefficiencies due to the remaining weaknesses of the cascade.

The alternative approaches for strengthening the care cascade exact their impact in different ways (Figure 4). The combination approach does not substantially reduce deaths among those who do not naturally present for HIV-testing (as this incurs significant cost), but reduces deaths among those who have tested by facilitating linkage, improving pre-ART retention and re-engagement, and by reducing deaths among patients in ART care by improving ART outreach. The immediate initiation approach also does not reduce deaths among those who do not naturally present for HIV-testing, but by placing all diagnosed patients onto treatment immediately, avoids the cost of pre-ART care and the potential for patients disengaging from care; as a result the majority of deaths occur among patients who initiated ART. In comparison, the UTT approach substantially reduces the number of persons that die from AIDS that were not diagnosed, due to the large outreach component (in the form of HBCT), but impact is moderated by the persisting large number of deaths mong those who start ART but subsequently disengage from care.

**Figure 3. DALYs averted and additional cost of care for individual interventions between 2010 and 2030.**



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| Intervention | DALYs Averted between 2010 and 2030 (million) | Additional Cost between 2010 and 2030 (million) (2013 USD) | Cost per DALY averted compared to baseline (ACER) |
| HBCT | 0.43 | $2,060.71 | $4,774.86 |
| Enhanced VCT | 0.14 | $232.11 | $1,683.18 |
| HBCT (with POC) | 3.47 | $3,067.88 | $884.44 |
| Facilitated Linkage | 0.45 | $160.15 | $356.31 |
| VCT POC | 1.43 | $527.20 | $367.51 |
| Pre-ART Outreach | 0.72 | $365.12 | $510.39 |
| Improved Care | 0.89 | $333.31 | $372.88 |
| POC CD4 | 1.35 | $498.27 | $368.44 |
| On-ART Outreach | 0.63 | $194.92 | $309.59 |
| Adherence | 0.31 | $131.90 | $425.75 |
| Immediate ART | 3.62 | $1,639.93 | $453.40 |
| Universal Test & Treat | 4.05 | $3,666.75 | $905.45 |

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| Intervention Combination | DALYs averted (millions) | Additional Cost Relative to Baseline (millions)  (2013 USD) | Cost per DALY averted compared to previous increment (ICER) | Cost per DALY averted compared to baseline (ACER) |
| ART Outreach | 0.63 | $194.92 | $309.59 | $309.59 |
| ART Outreach +  POC CD4 | 2.22 | $769.43 | $360.55 | $346.11 |
| ART Outreach +  POC CD4 +  VCT POC CD4 | 2.91 | $1,012.53 | $352.49 | $347.62 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage | 3.18 | $1,104.69 | $348.90 | $347.73 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach | 3.59 | $1,261.61 | $379.93 | $351.43 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach +  Adherence | 4.45 | $1,571.24 | $359.85 | $353.06 |

**Table 3. DALYs averted and additional cost of care for individual interventions between 2010 and 2030.**

**Table 4. DALYs averted and additional cost of implementing a combination of interventions between 2010 and 2030.**

# Discussion

**Figure 4. Care experience of deceased individuals who suffered an HIV-related death between 2010 and 2030.** Cost at the top of each bar is the total cost of care between 2010 and 2030 for each scenario.



Our results suggest that ART-programmes can be substantially enhanced to bring about greater health benefits by strengthening each part of the cascade or by shifting to treating HIV-infected persons immediately when they present to care. In contrast, a large expansion of treatment programmes, with the identified weaknesses in linkage and retention perpetuated, would not maximize health benefits in a resource-limited setting.

Improvements to the care cascade have previously been envisaged to be small-scale, feasible changes to the operations of a clinic that would yield large benefits, leveraging the enormous investment already made by ART to generate greater health outcomes{Cohen:2011kr, Herbst:2009ta}. However, we find that no individual intervention has a particularly large impact on patient outcomes (Figure 3), and this is due to the multifaceted nature of weakness in the current care cascade.

Instead we find that combinations of interventions at all parts of the cascade can have a large and cost-effective impact. Trials and other studies to date have only examined the impact of single interventions on the cascade{Govindasamy:2014fa, Barnighausen:2011cb}, as their experimental designs are not amenable to measuring the impact of a combination of changes simultaneously. However, studies investigating complete combinations are needed to confirm our findings. It may be that greater synergies accrue giving higher benefits and lower costs, or instead, that the increased complexity of operations leads to higher cost and fewer benefits.

An alternative major potential change would include the shift to immediate initiation of ART, removing the pre-ART monitoring part of the cascade{Granich:2009hv}. Attention has focused on the marginal therapeutic benefits to a patient of earlier initiation, but our findings show that there is potentially a large benefit in initiating patients immediately upon presentation, even if there is no additional direct clinical benefit. This is because this strategy mitigates the risk of losing a patient from the pre-ART monitoring phase, and therefore reduces the chance of further transmission and the risk of AIDS death before such a time as the patient may return to care. This is consistent with findings from the RapIT trial in South Africa, which found that patients were more likely to start ART sooner if they were offered treatment immediately when found to be eligible{RapidARTInitiation:2015tp}.

However, neither of these interventions – combinations of cascade interventions or immediate ART for those presenting – would reduce the risk of AIDS deaths among those not already diagnosed. Our model suggests that large numbers of deaths exist outside of the clinic among individuals never diagnosed (19%) and those who were diagnosed but never initiated treatment (57%). These results are in agreement with data from ALPHA sites in Rakai, Uganda, that indicate that around 20% of deaths in 2011 were among undiagnosed individuals and around 50% were among individuals tested but who never initiated ART[taken from *“HIV mortality in the treatment era” presented at BMGF 02/10/2013*]. Notably, many health data systems only account for individuals who have come into contact with the clinic, and therefore will fail to fully capture this driver of AIDS mortality (Figure 2). Monitoring and evaluation frameworks for the cascade should therefore seek to quantify the extent to which AIDS death fall among those undiagnosed and treatment guidelines should recognise testing as an integral part of the treatment programme.

Therefore, for the largest impact, substantial outreach is required to identify all HIV-infected individuals prior to needing ART. This is likely to attract significant costs, but the exact cost is unknown and even in well-documented existing care programmes costs vary between studies{Tagar:2014ed}. For instance, in an HBCT intervention trialled in Kwazulu-Natal, South Africa, there was a much higher probability of linkage to care than that seen in the AMPATH HBCT intervention{vanRooyen:2013gy,Genberg:2015cd}, making HBCT a highly cost-effective intervention in South Africa{Smith:2015wj}, but not in Kenya. Understanding the reason for these differences between programmes should be a priority as it is likely to reveal important ways in which the efficacy of HBCT can be maximised.

The variable performance of different HBCT programmes also highlights the wider issue that there are often substantial differences between two interventions falling under the same category, and that the observed impact and cost will also be a function of the underlying epidemic and programmatic context. Furthermore, we have demonstrated how the patterns of health-care seeking behaviour can modify the impact of interventions on population health, something that has not been readily apparent from empirical observation{Burns:2014jz}. It remains uncertain how these behaviours vary between location, and how they will interact with interventions now and in the future. For these reasons, it is hard to extrapolate the findings of different studies from different populations into a common framework, as we have had to do in this model. As a result, although each assumption about the interventions is based on a real study, our findings can only be taken to be directionally informative. Whilst the results presented are specific to the population in western Kenya served by AMPATH, we believe that our results will have the same broad relevance to the many other settings with large generalised epidemics in rural areas with a mature ART programme.

Findings from other modelling studies that have relied upon aggregated routine data to provide insight into care are in broad agreement with our results. For example, a similar modelling study focusing on South Africa has illustrated the potential impact and cost-effectiveness of a combination of interventions strengthening the cascade{Effectivenessofpot:2014wh}. Additionally, other modelling studies from Rwanda and South Africa have described the cost-effectiveness of immediate ART and treatment re-initiation interventions, respectively{EpidemiologicBenefi:2015vv,Klein:2014ho}. These differences in results so far highlight variations in the state of care by location, but also the risk of directly comparing model outputs due to potential inconsistencies in their approaches and assumptions.

This is a fast moving field. Last year, the UNAIDS 90-90-90 strategy set out three ambitious targets to be achieved by 2020 – 90% tested; 90% linked and retained; 90% virally suppressed{UNAIDS:2014vh}; some countries are already moving ahead to universal eligibility for ART{daSaude:2013wr, Towardsthesustaina:2014vk,UNAIDS:2014ta}; new data is emerging on clinical benefits of ART{EarlyARTandIPTin:2015tp}; many studies on cascade interventions are being reported{Barnighausen:2011cb, Govindasamy:2014fa}; and the WHO will shortly release new guidance for ART programmes. Synthesizing all these data with the perspective of improving health for the population, as we have done, is therefore especially important. Our results suggest that, there is considerable scope for programmes to generate even greater population health than they do currently and that alternative sets of strategies are available to them that may be consistent with their particular aims and budget.

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# References

# Figure Legends

**Figure 1.** Flow diagram representing the operational steps involved in navigating an ART-programme.

**Figure 2.** Care experience of patients suffering HIV-related deaths between 2010 and 2030. Figure 3. DALYs averted and additional cost of care for individual interventions between 2010 and 2030.

**Figure 4.** Care experience of deceased individuals who suffered an HIV-related death between 2010 and 2030.

**Table 1.** Summary of agreement between AMPATH data and the model.

**Table 2.** Summary of individual interventions designed to target various aspects of care.

**Table 3.** DALYs averted and additional cost of care for individual interventions between 2010 and 2030.

**Table 4.** DALYs averted and additional cost of implementing a combination of interventions between 2010 and 2030.

# Supporting Information

See Text S1.