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. Evidence suggests that these health losses are attributable to deficiencies in pre-ART and ART care. 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 western 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 estimated that the majority of AIDS related deaths in this population (57%) would be among persons that have been diagnosed with HIV but never initiated treatment. 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 interventions, based on earlier trial results, at individual points of the cascade or in combination. We find that no individual intervention is expected to provide a large benefit as it is confounded by other weaknesses both up and downstream. 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 (ICER $360; 0.5xGDP per capita in Kenya, $613); or a shift to providing treatment to all HIV-infected persons immediately upon presentation to care (3.62m DALYS averted between 2010 and 2030, and $453 per DALY averted). Either strategy would generate health more cost-effectively than an immediate expansion of testing and treatment, through a universal test and treat strategy (5.43m DALYs averted at $776 per DALY averted).

## Conclusions:

Our results suggest greater health benefits could be achieved in this setting by strengthening each part of the cascade, or by switching, as has been demonstrated to be feasible in earlier trials, to treating HIV-infected persons immediately when they present to care. In contrast, a radical expansion of treatment programmes, with the identified weaknesses in linkage and retention perpetuated, would not maximize health benefits in a limited-resource 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 as well as 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 >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. In South Africa, 200,000 AIDS-related deaths were estimated to have occurred in 2013{UNAIDS:2014ta}. Furthermore, a prospective cohort study in Uganda has revealed that the life expectancy of men and women initiating ART aged 20-24 years still falls below that of the general population (19.1 and 30.6 years vs. 41.6 years, respectively){Mills:2011gx}; therefore indicating, life-years are still being lost to AIDS{Collaboration:2008ed}. 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 appointments through which HIV-infected individuals must pass in order to benefit fully from ART, beginning with HIV testing, and ending with patients in a state of sustained viral suppression with regular monitoring. In 2011, Fox and Rosen highlighted how fewer patients reach each successive stage of HIV care{Rosen:2011ii}, and since then there have been many reports detailing the care cascade as it appears to operate in different countries{Nachega:2014ks, Nosyk:2013em, Kilmarx:2013iy, Fox:2014ch}. However, these studies have been limited by not having had 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 massive proliferation in innovative approaches to improve the care cascade{Govindasamy:2014fa, Barnighausen:2011cb}. These variously aim to improve testing, linkage to care, retention in pre-ART care and rates of viral suppression or retention in post-ART care. Many of these have been subject to a trial and there have been some remarkable successes. For example, a pilot using home-based counselling and testing (HBCT) with point-of-care (POC) CD4 in KwaZulu-Natal, South Africa, achieved 91% coverage of the community and linked 96% of newly diagnosed individuals within six months{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 interventions have had less success; one-on-one motivational sessions to group counselling in South Africa showed no significant difference in adherence or loss to follow up over the study period{Groupcounselingach:2010vo}. While important, these trials seldom measure the gains in population health (e.g. long-term effects and knock-on effects to persons not directly reached with an intervention), and largely focus on examining the impact of a new intervention at a single point in time. Additionally, trials have not been able to measure the combined impact of interventions targeting different areas of the cascade.

While it is increasingly recognised that strengthening of the cascade is required, and progress is being made in identifying possible interventions, there is a continued push for programmes to expand treatment and consider altering eligibility criteria to potentially all HIV-infected persons, and to increase active outreach to populations for testing (i.e. through ‘Universal Test and Treat’)

{Eaton:2013bv,Granich:2009hv}. 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 is 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 out of care, prior to testing, through an integrated household-based testing survey and intervention. 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 possible 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.

# 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. 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. For the years following 2001, the incidence rate in the model is re-calculated to reflect the growing number of persons on ART and to enable there to be the feedback from a successful ART programme reducing the number of new HIV infections.

Upon 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 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 assumed to also 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 has a suppressed viral load on ART, 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, but at a greater rate than ART-naïve patients.

Relevant 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 being compared to HIV prevalence estimates from AMPATH itself. A summary of model assumptions and data sources is shown in Table 1 with 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 involves seeking care voluntarily at a voluntary counselling and testing clinic (VCT), or in a healthcare setting through provider-initiated counselling and testing (PICT). Alternatively, the patient may be sought and diagnosed at home by a home-based counselling and testing team (HBCT). Diagnosis is followed by linkage to care, whereby an individual is seen by a clinician in an HIV clinic to be bled for a CD4 test in order to determine their eligibility for ART (critically ill new patients fast-track care and initiate treatment immediately if they are exhibiting WHO Stage III/IV symptoms). Patients then return after a month to receive their CD4 test results and learn of their eligibility for treatment. If a patient is not 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 undergo counselling before initiating ART, which can either result in patients adhering and becoming virally suppressed or failing to adhere. At each point in care, patients can disengage and become lost 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. We used these data to fully characterize the care cascade and then used these as input parameters to the model, or otherwise adjusted parameters in the model that were not directly observed in order to induce an agreement between the model and data (Table 2). The baseline scenario of the analysis represents the programme just prior the implementation of HBCT in this population.

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 3). As the effect size measured in trials, and that which would arguably be attainable differ, two assumptions for the effect size are used (a ‘maximum’ and a ‘realistic’ scenario).

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| Key Assumptions | Data Sources |
| For a given health state, the mortality rate on ART is less than the mortality rate off ART. | Natural history calibrated from clinical surveillance data. |
| Declining health drives care-seeking behaviour. | Calibration of events that make up HIV care from longitudinal dataset from AMPATH. |
| Individuals are exposed to a background rate of testing through VCT in addition to a rate of testing through PICT (dependant upon previous health care experience and health). | Disability weights sourced from the Global Burden of Disease Study 2010{Salomon:2012ib}. |
| Patients have the propensity to be lost from care at any stage. | Majority of costing data derived from the CHAI MATCH Study{Tagar:GTMxY-pi}. |
| If lost from pre-ART care, patients can re-engage at a later date. |  |
| If lost from ART care, patients will not re-engage with care (unless identified through an ART Outreach but patients can only re-initiate ART once). |  |

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 and HIV-related deaths averted, both with respect to a baseline ‘status quo’ programme similar in structure to AMPATH before the launch of household-testing.

Table 1. Key model assumptions and data sources.

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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 2. Summary of agreement between AMPATH data and the model.

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| **Aspect of care to be addressed** | **Intervention type** | **Intervention** | **Maximum Impact** | **Realistic Impact** | **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 of population. 100% linked to care. | 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 twice that of baseline. | 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)*** | Ever four years, 90% coverage of population. POC CD4 reduces risk of not linked to 0%. | 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 to 0% | 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, 100% of tested individuals lost from care are returned. | 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 to 0%. | 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, 100% of patients who have initiated ART and been lost from care are returned. | 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, all individuals adhere to ART and become virally suppressed. | 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. 100% linked to care) | 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 3. 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 drivers of AIDS-related deaths in the period 2010-2030 (Figure 2). The model finds that among all AIDS-related deaths, the majority (57%) 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 are 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 due to patients never testing or failing to attend the clinic following testing. It is therefore crucial that better systems of surveillance are developed that can include the outcomes of patients who never test or fail to link to care.

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 4). The ‘maximum’ scenario illustrates the total power of an individually applied intervention, while the ‘realistic’ scenario represents the achievable impact of interventions as is discussed below.

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%). HBCT with POC CD4, by increasing linkage, accrues nearly twice as many DALYs averted for a small increase in costs.

The two interventions that simulate 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, and benefit is accrued by eliminating the potential for losses from pre-ART care. The UTT intervention, by contrast, is much more costly as the outreach costs are estimated to be very large; yet, more impactful as 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 little benefit while attracting a high cost. This is due to the low level of VCT testing at baseline and the high cost associated with identifying an HIV-positive individual in the population. However, the model assumes that individuals testing through VCT are more likely to link to care than those testing through HBCT without further intervention. As a result, an intervention improving linkage to care for persons testing through VCT or PICT alone has limited impact.

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 is more beneficial than returning patients lost from care, as evidenced by the improved care and pre-ART outreach interventions. However, the benefit is marginal and in a realistic scenario, the cost per DALY averted compared to baseline (ACER) for improving pre-ART outreach is 26% less than improving care ($375 vs. $507, respectively).

Reducing loss to follow up between CD4 test and result by providing POC CD4 to all patients who have sucessfully engaged in pre-ART care has the same ACER as providing POC CD4 to all individuals testing through VCT ($369). The two interventions acting on patients already initiated on ART had very limited impact, this is due to upstream constraints resulting in only a small number of patients initiating treatment at baseline. As a result, returning all patients lost from care through an ART outreach strategy or ensuring all patients initiating treatment fully adhere to their medication provides restricted benefits to patient outcomes.

Under an alternative baseline assumption that people will not naturally seek care naturally as infection progresses, most interventions generate greater impact (Text S1). The two exceptions are the ART outreach and adherence interventions that are restricted by the number of patients that ever initiate ART at baseline. Under this alternate assumption, 18% of AIDS-related deaths are among patients who have initiated ART, compared to 24% in the ‘status quo’ model, hence these interventions have less of an impact. This alternative assumption illustrates how the marginal impact of interventions are limited by health-related care seeking behaviour, as most interventions become more powerful when this driver to care is removed. Additionally, the impact of each individual intervention is slightly weakened if transmission benefits are removed. This indicates that the majority of health benefits are accrued from direct effects reducing losses from care as opposed to the indirect impact of reducing incidence (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 did this for all ‘realistic’ intervention scenarios and 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 5). 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 not initiated treatment, interventions that increase linkage 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 ($353.06 vs. $905.37 ACER). This combination of cascade interventions is of similar cost to 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 again does not reduce deaths among those who do not naturally present for HIV-testing, but by placing all diagnosed patients onto treatment immediately, circumnavigates pre-ART care; yet, the majority of deaths occur among patients who initiated ART. In comparison, the UTT approach dramatically 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 among 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 | Scenario | DALYs Averted between 2010 and 2030 (million) | Additional Cost between 2010 and 2030 (million) (2013 USD) |
| HBCT | Maximum | 1.88 | $2,622.22 |
| Realistic | 0.43 | $2,060.71 |
| Enhanced VCT | Maximum | 0.62 | $898.44 |
| Realistic | 0.14 | $232.11 |
| HBCT (with POC) | Maximum | 3.53 | $3,127.03 |
| Realistic | 3.47 | $3,067.88 |
| Facilitated Linkage | Maximum | 0.82 | $294.73 |
| Realistic | 0.45 | $160.15 |
| VCT POC | | 1.43 | $527.20 |
| Pre-ART Outreach | Maximum | 1.83 | $689.03 |
| Realistic | 0.72 | $365.12 |
| Improved Care | Maximum | 1.95 | $983.26 |
| Realistic | 0.89 | $333.31 |
| POC CD4 | | 1.35 | $498.27 |
| On-ART Outreach | Maximum | 0.74 | $251.06 |
| Realistic | 0.63 | $194.92 |
| Adherence | Maximum | 0.70 | $183.54 |
| Realistic | 0.31 | $131.90 |
| Immediate ART | | 3.62 | $1,639.93 |
| Universal Test & Treat | Maximum | 5.43 | $4,216.30 |
| Realistic | 4.05 | $3,666.75 |

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| --- | --- | --- | --- | --- |
| Intervention Combination | DALYs averted (millions) | Additional Cost (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 4. DALYs averted and additional cost of care for individual interventions between 2010 and 2030.

Table 5. 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.



Our results suggest that ART-programmes can be materially 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, as has been demonstrated to be feasible in earlier trials{Cori:2014ip}. In contrast, a radical expansion of treatment programmes, with the identified weaknesses in linkage and retention perpetuated, would not maximize health benefits in a limited resource setting.

Improvements to the care cascade have long been hoped to be small, feasible changes to the operations of a clinic that would yield a large benefit, leveraging the enormous impact already made by ART to generate greater health outcomes{Cohen:2011kr, Herbst:2009ta}. Whilst we find this to be true to an extent, the multifaceted nature of the current cascade means that no individual intervention has a particularly large impact on patient outcomes (Figure 3). 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 particularly amenable to measuring the impact of a combination of changes simultaneously. However, by using a mathematical model it is possible to simulate combinations of interventions and estimate what the impact would be. All interventions modelled are based on real studies (Text S1), meaning that the impact projected may be realistic. 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 than expected. Further interventions are in the pipeline too, with discussion around making pre-ART more attractive to patients along with exploring its ancillary benefits{Geng:2010du}, which may further impact patient outcomes. Additionally, switching to providing immediate ART on a large scale has been discussed, but debate continues around the clinical benefits and the impact of such a strategy on transmission{Granich:2009hv, Boily:2012gg, Cori:2014ip}.

Ultimately, what we are finding here is that the pragmatic benefits of not losing patients who present to care, is powerful. This is consistent with the story from the RapIT trial in South Africa, which aims to evaluate the effect of immediate ART initiation on ART uptake. Early results illustrate that 88% of enrolled patients were virally suppressed six months after treatment initiation [*Rosen et al. (2015). Unpublished*]. This represents a very different approach as gains are brought about through circumnavigating the operational challenges of pre-ART care by removing it entirely. Under current assumptions, the strategy of implementing a combination of interventions, or providing immediate ART, have nearly the same impact and cost, so both can be recommended. Yet, the combination of interventions results in fewer person-years spent on ART, reducing the likelihood of resistance through failure to adhere to treatment{Oyugi:2007fs}.

However, as many data systems only account for individuals who have come into contact with the clinic, they fail to fully capture the state of care in the community (Figure 2). The population perspective reveals that the loci of many HIV-related deaths, when clinic-focussed interventions are considered, will not bring about the largest impacts. Large numbers of deaths exist outside of the clinic among individuals never diagnosed (19%) and those who were diagnosed but failed to initiate ART (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[*Emma Slaymaker (can’t find the relevant paper)*]. This reinforces our results, indicating that mortality is chiefly occurring outside the clinic. Monitoring and evaluation frameworks for the cascade, as well as treatment guidelines should consider this point carefully; the effectiveness of a treatment programme is only as good as that of the HIV-testing programme.

Yet, neither providing immediate ART or the proposed combination of interventions would address this issue. For the largest impact, massive outreach is required to identify all HIV-infected individuals prior to death, but this is likely to incur substantial costs. Additionally, an equity dimension should be considered; should programmes continue to improve care for those that are more readily able to access it? Or alternatively bring the whole population to a standard of care? The exact cost of either strategy is unknown and even in well-documented care programmes costs vary between studies{Tagar:2014ed}. Ultimately, costs depend on demand creation together with how attractive and convenient HIV-testing and linkage can be made. Therefore to ensure future costs are minimised, further insight into how costs accrue in HIV care systems is required.

For instance, an example of an HBCT intervention trialled in Kwazulu-Natal, South Africa, achieved higher linkage rates at a lower cost than assumed here{vanRooyen:2013gy}. The intervention involved home-based HIV-testing followed by immediate POC CD4 testing and follow-up visits to facilitate linkage and adherence to care{vanRooyen:2013gy}. At $17.32 per person tested (without ART costs), this intervention is highly cost-effective in comparison to the 0.5xGDP threshold for South Africa ($3,256 USD 2013). The wider issue is that there are often substantial differences between two interventions of the same name, as no two interventions are identical{Barnighausen:2011cb}. Additionally, extrapolating trial results to other settings remains challenging due to the fundamental causes of impact and cost, together with the intricate balance between an HIV care system and the underlying health care seeking behaviour of the population. The motivating stimuli driving HIV-infected individuals to seek care are not yet fully understood and this confounds the estimated impact of our interventions. As we demonstrate, in the absence of patients naturally seeking care when they are sick, interventions aimed at retaining patients in care have a larger impact. We were able to make inferences regarding care-seeking behaviour by confronting the model with data from AMPATH on, for example, the proportion of patients initiating ART at enrolment to care over time. With progress being made in other fields{Buregyeya:2011fi, Salaniponi:2000tc, Pronyk:2001uk}, it is hoped that new insights into HIV health-care seeking behaviour will follow as this is currently a source of uncertainty and remains a priority to strengthen the impact of health systems more generally{Burns:2014jz}.

For progress to be made in assessing the current state of care along with strategies to resolve deficiencies in other settings, individual-level longitudinal data similar to that provided by AMPATH will be required. In general terms, extrapolation of our results to other settings is possible, if compared to a mature ART programme with similar trends in care seeking behaviour. However, as care systems evolve, the relative impacts and costs of interventions change over time, and are modulated by the interplay between health care seeking behaviour and the logistics of care. With limited data of this type currently available, insight into the state of care in other sub-Saharan countries is restricted. Findings from other modelling studies that have relied upon aggregated routine data to provide insight into care are in broad agreement with our results; although, these studies have not been able to explore the same range of intervention options or utilise high resolution data from a single care programme. For example, a similar modelling study recently found that improving the re-initiation of ART in a treatment programme in South Africa was a highly cost-effective intervention{Klein:2014ho}. This leads us to speculate that a larger proportion of individuals are initiating ART in South Africa as our model results indicate that a similar intervention was not particularly impactful. However, this type of intervention becomes nearly 5-fold more powerful if upstream care is flawless[*results not shown (in Leaks.docx)*].

With many countries moving ahead with plans to further expand HIV treatment eligibility guidelines, it is important to evaluate the current state of care to improve the efficiency of care systems and maximise the benefits of ART. For example, Brazil is moving towards a Treatment as Prevention strategy involving universal testing and treatment to all HIV-infected individuals irrespective of CD4 count{daSaude:2013wr, Towardsthesustaina:2014vk}, and Rwanda has plans to provide immediate ART to all infected individuals seeking care [can’t find a reference for Rwanda].

Additionally, with the UNAIDS 90-90-90 strategic paper detailing three ambitious targets to be achieved by 2020, there is an urgent need for countries to improve all aspects of care at once{UNAIDS:2014vh}. While WHO treatment guidelines predominantly focus on treatment eligibility thresholds and patient monitoring, based on clinical evidence, they do not include recommendations for HIV-testing{WorldHealthOrganization:2013we}. Our results suggest that, programmes need to either systematically strengthen care by utilising a combination of interventions; or, radically simplify care and provide immediate treatment to all presenting patients. Additionally, further impact can be sought through large outreach programmes, but expanding outreach whilst upstream weaknesses remain risks failing to achieve maximum impact from investment. Consequently, we feel that this analysis will help shape the discourse around the cascade and interventions that are formulated, evaluated and rolled-out to improve the impact of ART programmes in sub-Saharan Africa.

# Acknowledgements

# References

# Figure Legends

***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).*

***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).*

***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*** *– Key model assumptions and data sources.*

***Table 2*** *– Summary of agreement between AMPATH data and the model.*

***Table 3*** *– Summary of individual interventions designed to target various aspects of care.*

***Table 4*** *– DALYs averted and additional cost of care for individual interventions between 2010 and 2030.*

***Table 5*** *– DALYs averted and additional cost of implementing a combination of interventions between 2010 and 2030.*

# Supporting Information

See Text S1.