Evaluating Strategies to Improve HIV Care Outcomes in Kenya

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# Abstract (300 words)

## Background:

With expanded access to antiretroviral 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 ART-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. The model suggests that most AIDS-related deaths (57% between 2010 and 2030) in this population are among persons that have been diagnosed with HIV but never initiated treatment. Other predicted drivers of death are late initiation (9%) and disengagement with care following initiation of ART (12%). We used the model to simulate the cost and impact of alternative interventions, based on earlier trial results. We find that no single intervention to improve the cascade to care is expected to have a large outcome because any single intervention is confounded by other weaknesses both up- and down-stream. 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; 0.5GDP per capita=$613); or a shift of providing treatment to all HIV-infected persons immediately when they present for care (3.62m DALYS averted between 2010 and 2030 and $453 per DALYS averted). Either approach would generate health more cost-effectively than an immediate expansion of testing and treatment (universal test and treat) without strengthening the care cascade.

## Conclusions:

Our results suggest that ART-programmes in Kenya can be enhanced to bring about greater health benefits by strengthening each part of the cascade or 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 weakness in linkage and retention perpetuated, would not maximize health generated with limited resources. International guidance ART should reflect these alternative routes to program strengthening, recognise outreach as an integral part of a treatment intervention, and encourage country programmes to evaluate the costs and impact of ART expansion as well as evaluating 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 deaths each year. In South Africa, 200,000 AIDS-related deaths were estimated to have occurred in 2013{UNAIDS:2014ta}. Further, 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 the era of wide-scale ART availability, why are such large health losses continuing and what can be done to improve the population health that is generated by ART programmes?

The reasons for continued health losses to HIV have not been well understood but attention has been focussed on the ‘care cascade’{McNairy:2012dg}. This is 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{Rosen:2011ii}. And since then, there have been many detailed reports for different countries detailing the care cascade as it appears to operate in particular 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 would typically be focussed on the subset of the population that presents to a clinic, and are therefore blind to the outcomes of patients that never engage or disengage from care.

During the last few years there has also been a massive proliferation in innovative approaches to improving the care cascade. These variously aim to improve testing, linkage to care, retention in pre-ART care, 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, in South Africa van Rooyen et al. trialed a home-based counselling and testing (HBCT) intervention achieving 91% coverage of the community and 96% of newly diagnosed individuals linked to care within six months{vanRooyen:2013gy}. Jani et al. were able to reduce pre-ART loss to follow up 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 through a decentralising intervention that involved transitioning stable patients on ART from a hospital to a primary health care facility{Long:2011cx}. Although, some interventions have had less success such as the addition of one-on-one motivational sessions to group counselling in South Africa that had no significant difference in adherence or loss to follow up during nine months of followup{Groupcounselingach:2010vo}. However, these trials seldom measured the gains accrued in population health (e.g. longer-term effects, and knock-on effects to persons not directly reached with an intervention) and have had to largely focus on examining the impact of a new intervention at a single point in time, and have not been able to measure the combined impact of interventions as different part of the cascade.

At the same, there has been a push to continue the rapid expansion of treatment, including expanding the eligibility criteria for treatment (to potentially all HIV-infected persons) and to increase active out-reach to populations for testing (i.e. ‘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 that is the right approach given the apparent fragility of some current systems has been unclear and 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 mortality in the populations they serve, and having to decide which of the potential ‘care cascade’ interventions should be prioritised in order to generate the greatest gains in population health for the available resources have had little data to guide them.

However, mathematical models combined with longitudinal data from real programmes can offer a way to draw conclusions around the way in which programmes should develop. The AMPATH programme furnishes unique data of 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 experiences of care for the HIV-infected patients. With this, we produce the first estimates of the drivers of AIDS mortality in a population benefitting from a mature ART programme. We are then able to use the model to estimate the cost and and impact of possible interventions, in isolation and in combination, examining the impacts on patient health and downstream benefits simultaneously. In this way, we are able to come to broad recommendations about how programme managers can modify their progammes to maximise the health generated.

# 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 assumption; (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 assumption***

The microsimulaton model represents births, ageing and death among the population of western Kenya, using data from 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 between 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 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. The rates of transitioning are informed through fitting the model to surveillance data on CD4 reconstituation rates{Lawn:2006ht} together with mortality rates stratified by CD4 count and WHO stage from the IeDEA Southern Africa{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 UNIADS 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 KAIS 2007 and 2012 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 for each HIV-infected person (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 are able to 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 AIDS-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 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 charactersize 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.

The cost of the ART programme at baseline is 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 cost of ART care, the cost of pre-ART clinic visits and CD4 lab-based tests{Tagar:GTMxY-pi}.

1. ***Interventions on the care cascade***

Interventions in 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 different trials, and that which would arguably be attainable, differed two assumptions for the effect size (a ‘maximum’ and a ‘realistic’) are used.

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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 impact 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 in which a programme similar to AMPATH before the launch househld testing programme, is maintained indefinitely.

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% 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 deaths in the period 2010-2030 (Figure 2). The model finds that among all HIV-related deaths, the majority (57%) occur in individuals who were diagnosed with HIV but who did not ever start treatment (Figure 2(a)). A further 19% of AIDS deaths are among persons who never engaged with care prior to death. With the remainder of AIDS deaths were among those who started ART.

Most data systems, however, do not benefit from such a holistic view of the population and are instead based upon only those who attend a clinic at least once (Figure 2(b)). In that case, 33% of all AIDS 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 outcomes of patients who never test or do not link to care at all.

Figure 2. Care experience of patients suffering HIV-related deaths between 2010 and 2030.



## 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).

Broadly, the impact 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 other interventions. The intervention to provide 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 is much more costly and somewhat more impactful because the outreach costs are estimated to be very large but the population coverage of ART can reach higher levels with an outreach intervention such as HBCT.

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 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 provided restricted benefits to patient outcomes.

Under an alternative baseline assumption that people will not seek care naturally at a faster rate as infection progresses, most interventions generate greater impact (results in 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 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.

## 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 (Table 5).

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 (Table 4). Importantly, this combination of intervention includes elements that act on each part of the cascade. As the major driver of AIDS deaths in this population were 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 the almost the same impact on reducing deaths (37% vs. 38% of AIDS deaths at baseline) and averting DALYs (4.45m vs. 5.08m) as Universal Test and treat intervention but is estimated to cost only approximately 44% as much. The 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 interventions is a result of the collection of intervention operating synergistically, whereas the UTT and Immediate ART intervention operate with inefficiencies due to the remaining weakness 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 (millions) | Additional Cost between 2010 and 2030 (millions) (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 | 5.59 | $4,267.86 |
| Realistic | 5.08 | $4,077.49 |

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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) | Percentage of maximum attainable impact achieved |
| ART Outreach | 0.63 | $194.92 | $309.59 | $309.59 | 6% |
| ART Outreach +  POC CD4 | 2.22 | $769.43 | $360.55 | $346.11 | 20% |
| ART Outreach +  POC CD4 +  VCT POC CD4 | 2.91 | $1,012.53 | $352.49 | $347.62 | 26% |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage | 3.18 | $1,104.69 | $348.90 | $347.73 | 28% |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach | 3.59 | $1,261.61 | $379.93 | $351.43 | 32% |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach +  Adherence | 4.45 | $1,571.24 | $359.85 | $353.06 | 39% |

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, as has been demonstrated to be feasible in earlier trials{Govindasamy:2014fa, Barnighausen:2011cb}, or by shifting to treating HIV-infected persons immediately when they present to care. In contrast, a radicial expansion of treatment programmes, with the identified weaknesses in linkage and retention perpetuated, would not maximize health generated with limited resources.

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 very large impact on patient outcomes. Trials and other studies to date, have only examined the impact of single interventions on the cascade{Govindasamy:2014fa, Barnighausen:2011cb}, as those experimental designs are not very ameanable to measuring the impact of combinations of changes simultaneously. However, witih the aid of a mathematical model we can see how attractive a combination set of interventions potentially is. 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 accure giving higher benefits and lower costs, or, instead that the increased complexity of operations leads to higher cost and less benefits than expected. Further interventions are in the pipeline too, with discussion around making pre-ART more attractive to patients along with its ancillary benefits{Geng:2010du}, which may bring additional impact on 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). Confidential. 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 strategies of implementing a combination of interventions or providing immediate ART have nearly the same impact and cost, so both can be recommended on this basis.

However, as many data systems only account for individuals who have had 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 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 before death (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 ~50% were among individuals tested but who never initiated ART[*Emma Slaymaker (only going off the Paris slides here – 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 and all HIV-infected individuals prior to death, but this will 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 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. To ensure future costs are kept low improvements need to be made in understanding how costs accrue in HIV care systems.

For instance, another example of an HBCT intervention trialled in Kwazulu-Natal, South Africa, achieved 91% coverage of the community and within six months, 96% of newly diagnosed individuals had been linked to care 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 ($3,256 USD 2013). In contrast, an HBCT intervention trialled at another AMPATH site in Kenya, achieved coverage of 88% of the population, but among newly diagnosed individuals only 15% had been linked to care over a median of 3.4 years since diagnosis{Genberg:2015cd}.

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 underlying 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 enrollment 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 majority 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 data provided by AMPATH will be required. In general terms, extrapoliation of our results is possible as in a mature ART programme dropout from ART is common [REFERENCE]. However, the balance of care changes over time, as the relative impact and cost of interventions are modulated by the interplay between health care seeking behaviour and the logistics of care.

While a mathematical model can demonstrate the impact of a combination of interventions, it remains to be seen how such a strategy would be implemented by a real-world ART programme. For instance, it may be preferable to distribute intervention implementation over time as part of a graded response.

* Extrapolation to other places.--- perhaps possible in general terms. We have benefit from the detailed AMPATH data but the general picture of a mature program with relatielt frequency care seeking and drop-out from ART is common. However the balance will be expected to change over time, and the relativr impact and costs of itnerventions will be modulated by health care seeking behaiorund and local conditions, will probably dominate the analysis.
* Findings of other moelling work, which relied on routinely available data on national programs at aggregated level, have been in broad agreement – although these have not been able to examine the same range of itnerventions options that we have nor be grounded in the data from the operations of a single program, nor benefit from the linkage of longitudiianl data from community outreach and clinical data.
* Many Contries moving ahead (e.g. Brazil – UTT: Rwanda; Imm ART) and it will be import to evaluate.
* UNAIDS 90-90-90 thing – urgent aim for everything all at once. WHO treatment guidelines have been focussed on threshold for initation and paient monitoring and with recommendations focussed on clinical evidence. WHO tretmet guidelines not include testing. But our results suggest that, in fact, programs need to either strengthen thieir cascade, especially on the pre-ART side; or, radically simplify care and provide treatment to all presenting; and then to achieve the greatest impact to include large outreach programs. Expandiing outreach whilst weaknesses remains risks faling to get maximum impact from invesmtnet.

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These results indicate that within an ART programme in Kenya and under our baseline conditions, care is suboptimal. When assessing HIV-related deaths at the community-level, among all individuals, the majority of deaths were attributable to patients who never initiated ART and in particular to patients who were aware of their HIV-status but due to failings of pre-ART care, did not initiate treatment (figure 2, left). However, when the same scenario was considered from the clinic-level, among all individuals who had contact with the clinic yet suffered an HIV-related death (figure 2, right), the 19% of individuals who never engaged with care (from the left-hand figure) was absent. Additionally, the clinic-level view indicates that 35% of deceased patients had initiated ART; however, stepping back to the community-level view, only 24% initiated ART prior to death. These results highlight the major limitation of clinic-level data: only patients who contact the clinic are accounted for. Consequently, masking a major deficiency in care and cause of mortality.

Intervening at various points in care with individual interventions illustrates that HIV-testing and pre-ART retention are suboptimal, as interventions targeting those areas, such as HBCT or Improved Care, were highly impactful (figure 3). In contrast, removing pre-ART care all together (Immediate ART) and additionally actively seeking individuals (Universal Test & Treat) averted the most DALYs between 2010 and 2030(3.62m and 5.59m DALYs averted, 32% and 50% of MAI, respectively); however, these interventions were the most expensive to implement($1.64b and $4.27b, respectively). From analysis of these individual strategies, no single large-impact low-cost intervention was identified, with high impact interventions having a high cost per DALY averted and low cost interventions having a low cost per DALY averted. Additionally, we identified a combination of six interventions that when applied simultaneously improved patient outcomes at a cost of $353 per DALY averted compared to baseline. This combination strengthened care at multiple points and is potentially as impactful as the Universal Test and Treat strategy but with a lower average cost-effectiveness ratio.

This work indicates that it is imperative for ART programmes to evaluate patient outcomes from the population perspective. The clinic-level view is biased, as only individuals who have had contact with the clinic are accounted for. Thus, to fully understand where deficiencies in care are leading to lives being lost to HIV, the entire community must be fully represented. This poses significant challenges for HIV care providers, as assessing community-level outcomes, particularly among individuals with no prior engagement in care, is both financially and logistically testing. Additionally, as ART programmes consider intervening to improve care, many currently available interventions only target one aspect of care{Kilmarx:2013iy, Barnighausen:2011cb,Govindasamy:2014fa}. Our results deduce that a single intervention strategy provides limited benefit, as any individual interventions enacted will be attenuated by downstream deficiencies in care, and also limited by any upstream constraints. For instance, interventions targeting linkage to care will be constrained by the number of individuals who attempt to link and further capped by downstream losses from pre-ART and ART care. Thus as our results corroborate, care must be strengthened by intervening at multiple points with a combination of interventions to fully realise the benefits afforded by ART. Although interventions utilising an immediate ART strategy provide the largest improvement in patient outcomes, these gains are brought about through circumnavigating the operational challenges of pre-ART care by removing it, potentially depriving patients of its ancillary benefits{Burtle:2012kw,Govindasamy:2014fa}.

This model was predominantly calibrated using a longitudinal dataset provided by AMPATH of western Kenya. However, only the clinical elements of HIV care were calibrated to AMPATH data. National estimates of incidence were used to drive and replicate the epidemic before model results were then validated against further national estimates of prevalence, AIDS-related deaths and ART coverage{Spectrum:tl, KAIS:2014ux, NASCOP:2012tp}. Additionally, our baseline scenario does not include a HBCT component unlike the current programme at AMPATH. Consequently, this model deviates from directly describing the state of care at AMPATH to more broadly capturing the probable state of care in Kenya. Thus, the generalisability of these results to other ART programmes and elsewhere in sub-Saharan Africa remains open to debate. With limited data of this type currently available, insight into the state of care in other sub-Saharan countries is restricted. 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)*]. In another mathematical model investigating HIV testing strategies in South Africa, Bendavid *et al*. demonstrate that implementing a universal test and treat strategy with enhanced linkage and retention in care would nearly double the survival benefits of a strategy with current linkage and retention rates{Bendavid:2010gu}. Status quo linkage rates were 67% compared to 60% in our results, further illustrating the importance of successfully linking patients to care{Bendavid:2010gu}.

While this work discusses individual interventions targeting specific aspects of care, there are often substantial differences between two interventions of the same, or similar, name{Barnighausen:2011cb}. For example, in regard to HBCT, two such interventions have been trialled in different locations in sub-Saharan Africa with contrasting results. An intense HBCT intervention was tested in Kwazulu-Natal involving home-based HIV-testing followed by immediate POC CD4 testing and follow-up visits to facilitate linkage and adherence to care{vanRooyen:2013gy}. This intervention achieved 91% coverage of the community and within six months, 96% of newly diagnosed individuals had been linked to care{vanRooyen:2013gy}. In contrast, an HBCT intervention trialled at another AMPATH site in Kenya, achieved coverage of 88% of the population, but among newly diagnosed individuals only 15% had been linked to care over a median of 3.4 years since diagnosis{Genberg:2015cd}. The difference in linkage rates between the two interventions is likely a result of the former involving a combination of POC CD4 testing and follow-up visits to motivate individuals to link. Together with our results, demonstrating the limited impact of HBCT in the absence of POC CD4 or perfect linkage, this provides evidence to suggest that HBCT alone is not capable of generating the impact that it was designed to achieve.

Overall, the results of these analyses resonate with the health losses reported in many ART-programmes and thus reaffirm the link between patient outcomes and suboptimal care. When considering the distribution of care experience among HIV-related deaths in the entire population(figure 2, left), 19% of individuals were never diagnosed and 57% failed to initiate ART before death. These results are in agreement with data from ALPHA sites in Rakai, Uganda, which indicate that around ~20% of deaths in 2011 were among undiagnosed individuals and ~50% were among individuals tested but who never initiated ART[*Slaymaker (only going off the Paris slides here – can’t find the relevant paper)*]. This reinforces our results, indicating that mortality is chiefly occurring outside the clinic.

Additionally, we illustrated that no single intervention provided large gains in patient outcomes without incurring significant costs. The most impactful intervention, Universal Test & Treat, averted 5.59m DALYS at a cost of $4.27b ($763.86 per DALY averted). However, when compared to the maximum attainable impact scenario, in which all infected individuals are placed onto ART from 2010 onwards with perfect adherence and retention in care, the Universal Test & Treat intervention averted 50% of the MAI. This scenario illustrates the lowest number of DALYs that will accrue given baseline care prior to 2010, as averting 100% of DALYs accrued between 2010 and 2030 at baseline is an impossibility. Obtaining an MAI value higher than 50% would require the combination of a Universal Test & Treat strategy with ART adherence and outreach interventions to prevent long-term losses from ART care. However, through the use of a combination of interventions targeting both pre-ART and ART care, 88% of the DALYs averted by the Universal Test and Treat intervention can be achieved at 44% of the cost per DALY averted (table 3). Yet, this combination of interventions was only able to avert 39% of the maximum attainable impact; due to the lack of any interventions targeting HIV-testing, as these have a high cost per DALY averted (table 3). Consequently, this indicates that intervening at multiple points to strengthen care is almost as effective as removing pre-ART care in its entirety, such as in the Immediate ART or Universal Test & Treat strategies, but without depriving patients of the ancillary benefits provided by pre-ART care. However, little is known about the long-term impacts of immediate ART on patient retention and adherence; but the recently published early results of the RapIT trial in South Africa evaluating the effect of immediate ART initiation on ART uptake illustrate that 88% of enrolled patients were virally suppressed six months after treatment initiation[*Rosen et al. (2015). Confidential. Unpublished*].

Interestingly, the distribution of care experience among deceased individuals when the combination of interventions was compared to a Universal Test & Treat strategy highlights, how both strategies significantly reduced HIV mortality in comparison to baseline, but through different mechanisms(figure 4). We see that the combination of interventions was able to reduce the proportion of HIV-related deaths among individuals who were diagnosed but never initiated ART, but as none of the interventions enhance HIV-testing a similar proportion of individuals decease, without being diagnosed, to the baseline scenario. In contrast, in the Universal Test & Treat intervention only 13% of individuals who suffered an HIV-related death never initiated ART; with the vast majority (51%) lost from ART care before death. Therefore, the total person-time spent on ART by individuals in the Universal Test & Treat intervention exceeded that of individuals in the combination intervention scenario, this is reflected by the increased cost of Universal Test & Treat and the larger proportion of cost that is attributable to ART care. Consequently, the combination of interventions results in fewer person-years on ART, reducing the likelihood of resistance through failure to adhere to treatment{Oyugi:2007fs}. An alternative category of interventions recently hypothesised to improve patient outcomes and reduce costs, is that of tiered care, using patient strata to determine the provision of care services. For example, Babigumira *et al.* (2011), implementing a task-shifting intervention for eligible patients at an HIV clinic in Kampala, Uganda{Babigumira:2011gg}. Eligibility criteria selected adherent, healthy randomised patients on ART to switch from monthly physician visits to seeing a physician every six months and picking up medication from a pharmacy on a monthly basis. No significant difference in clinical outcomes was observed and the annual cost of care decreased by 20% for patients attending physician visits every six months{Babigumira:2011gg}. This type of tiered intervention, selecting adherent patients to be monitored more infrequently, illustrates how care can be stratified between patients.

The motivating stimuli driving HIV-infected individuals to seek care are not yet fully understood. 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{Burns:2014jz}. Furthermore, the generalisability of these results to other settings remains undetermined; but for progress to be made in assessing the current state of care along with strategies to resolve deficiencies, individual-level longitudinal data similar to data provided by AMPATH will be required. While a mathematical model can demonstrate the impact of a combination of interventions, it remains to be seen how such a strategy would be implemented by a real-world ART programme. For instance, it may be preferable to distribute intervention implementation over time as part of a graded response. Finally, the estimates of costs used in this model are predominantly based on findings from a large-scale multi-country analysis, but the true scalability of these costs and their representation of the cost of intervention execution are debatable.

Our results indicate that in Kenya, the effectiveness of current ART-programmes can be improved. While interventions targeting HIV testing and pre-ART retention were highly impactful, losses from care occurred throughout, leading to suboptimal treatment outcomes for patients. In this setting, our results show that a combination of interventions targeting multiple points of care is a cost-effective way to strengthen current ART-programmes. 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.*

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

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

***Table 3*** *– DALYs averted and additional cost of care for individuals 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 appendix.