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, HIV-related life expectancy has increased, yet life-years are still lost to untested and untreated individuals. Evidence suggests that these health losses are attributable to deficiencies in pre-ART and ART care. We aimed to assess the state of a current ART-programme in Kenya and the potential for interventions to improve patient outcomes.

## Methods & Findings:

We constructed an individual-based mathematical model to describe the care experience of HIV-infected adults in an ART-programme in Kenya. The model simulates natural HIV progression and mortality through CD4 cell count stages and clinical symptoms. We calibrated the model to a longitudinal dataset from The Academic Model for Providing Access To Healthcare (AMPATH) describing the routes into, losses and outcomes of care in western Kenya. We assessed care at baseline, before exploring the impact of 12 interventions acting on different aspects of pre-ART and ART care, applied individually or in combination to determine strategies to improve outcomes. We quantified health outcomes in terms of disability-adjusted life years (DALYs) averted and additional cost relative to baseline between 2010 and 2030. Our results indicate that in Kenya care is suboptimal at multiple points, thus restricting the impact of interventions targeting a single point of care. With the majority of HIV-related deaths occurring among diagnosed individuals who never initiated treatment (57%), we identified that a combination of interventions targetting multiple points of care produces 88% of the impact of a Universal Test & Treat strategy that circumnavigates pre-ART care, at 44% of the cost per DALY averted ($353 vs. $803 per DALY averted, respectively).

## Conclusions:

Our results suggest that ART-programmes in Kenya can be enhanced to bring about greater health benefits. In this setting, as care is not suboptimal at one particular point, a combination of interventions targeting multiple points in care may be a more cost-effective solution than a single-point intervention.

# Introduction

The predominant focus of HIV funding over the last decade has been on improving access to antiretroviral therapy (ART); with the latest reports indicating that over nine million people are receiving ART in sub-Saharan Africa{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, 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 HIV in this thunderous epidemic{Collaboration:2008ed}.

The reasons for continued health losses to HIV are numerous. Firstly, the on-time identification of infected individuals in many resource-limited settings is scarce{Drain:2013iv,Sabin:2004uy}. Timely diagnosis is defined as alerting an individual to their serostatus prior to that individual becoming eligible for treatment; yet, data from Uganda indicate that almost half of all infected individuals newly diagnosed were already eligible for treatment, and therefore detected late{Wanyenze:2011gz}. Secondly, late diagnosis is followed by late initiation of treatment; with many studies reporting patients initiating ART with CD4 counts far lower than treatment guidelines recommend{Boulle:2014uj,Lahuerta:2012hi, Lahuerta:2013tk,Nash:2011ki}. The major consequence of late ART initiation, is an observed increase in HIV-related mortality, negatively correlating with CD4 count at the time of initiation{Johnson:2013co}. Thus, from the viewpoint of the clinic, late treatment initiation is the major driver behind HIV-related mortality in ART programmes. Current data now indicates that the hazard ratio of mortality for patients initiating ART with CD4 counts ≥200 vs. <25 cells per μl is 0.21 (95% CI, 0.17 – 0.27){May:2010ee}. However, mortality is likely to be underestimated due to significant unreported deaths among patients lost to follow up{Brinkhof:2010gr}. Additionally late treatment initiation likely results in onward transmission until viral suppression can be achieved{Lahuerta:2013tk,Cohen:2011kr}.

This discrepancy between treatment access and eventual patient outcomes allude to inefficiencies within HIV care systems{Gardner:2011de}. Moreover, accumulating evidence suggests that HIV care is suboptimal not at one particular point, but across the entire spectrum of care, as “cascading losses” have been reported throughout ART programmes{Rosen:2011ii,Fox:2014ch}. A review by Rosen and Fox in 2011 highlighted the scale of the issue in sub-Saharan Africa; illustrating that on average only 18% of patients are retained from HIV testing until ART initiation{Rosen:2011ii}. Results indicated that, 59% of patients were retained from HIV testing to receipt of CD4 test results, whereupon 46% of remaining individuals were retained until ART and finally 68% of the remainder were retained up to treatment initiation{Rosen:2011ii}. While among those patients initiating ART, recent estimates from South Africa indicate that 81% were retained in care two years after starting treatment{Fox:2014ch}.

The milestones that must be achieved to realise optimal care outcomes begin with diagnosis. Positive HIV-testing to confirm infection is followed by a blood draw for CD4 count measurement to assess the state of disease progression and eligibility for treatment. Once deemed eligible for treatment, ART is initiated and must be adhered to thereafter. However, the operational steps required to deliver these milestones are complex. Initially, once diagnosed individuals need to be linked to pre-ART care, meaning they must attend a clinic to be bled for a CD4 test. Consequently, there is a risk they may not attend. Kranzer *et al.* have shown that in South Africa, 37.4% of individuals tested failed to link to care within six months of diagnosis{Kranzer:2010hp}. Furthermore, after linking to care and receiving a CD4 test, the patient is advised to return at a later date to receive the results and learn of their eligibility for treatment. The time delay is due to CD4 tests being predominantly lab-based requiring central processing{Larson:2012dq}. A utility cost is often incurred when travelling to the HIV clinic as patients travel long distances from remote areas to attend and often receive no immediate therapeutic benefit{Geng:2010fh, Yu:2007wh, Ware:2009id}. This represents another opportunity for patients to be lost from care, as demonstrated by a study in South Africa where 65% of patients failed to return to receive CD4 test results within 12 weeks of the test{Larson:2010dz}. When receiving CD4 test results, if the patient is not immediately eligible for treatment, they are asked to return after a period of time for a follow-up test. Patients may endure multiple rounds of CD4 tests and clinic visits prior to ART initiation. This can result in loss from care, as shown by findings from Kenya, in which a CD4 count of >200 cells/μl at pre-ART enrolment resulted in a 3.49 fold increase in the odds of being lost from care{Geng:2010du}. Confirmatory CD4 test results indicating ART eligibility are followed by counselling and treatment initiation. ART initiation marks the start of lifelong ART care, where a successful treatment outcome can be achieved through retention in care and adherence to ART. However, long-term retention in ART care is also suboptimal as was illustrated by a review of over 200 thousand individuals across sub-Saharan Africa, demonstrating average retention three years after treatment initiation to be just over 70%{Fox:2010gt}. Additionally, a meta-analysis of 12 sub-Saharan countries has estimated that only 77% of patients are achieving adequate adherence to ART, increasing the risk of mortality and resistance development among those failing to adhere{Gardner:2009fb,Nachega:2006bx,Mills:2006gf}.

With poor patient outcomes being linked to structural weaknesses in ART programmes, providers have begun to intervene and improve care. For example, interventions aimed at improving the uptake of HIV-testing have targeted individuals through setting up voluntary counselling and testing (VCT) clinics in accessible sites and by establishing provider-initiated counselling and testing (PICT) by incorporating HIV counselling and testing into healthcare services{Obure:2012fb, Thielman:2006fm}. Home-based counselling and testing (HBCT) interventions also aim to improve testing uptake{Menzies:2009fs}. This type of intervention involves home-visits by care workers who administer counselling and rapid HIV-tests to consenting participants{vanRooyen:2013gy}. Infected individuals learn of their status immediately and are then encouraged to attend a clinic for CD4 testing{Kimaiyo:2010tq}. HBCT has been shown to be a powerful diagnostic tool as individuals are sought out rather than seek care themselves; although, the impact of HBCT on linkage to care remains limited{vanRooyen:2013gy, Genberg:2015cd}. A method for increasing linkage to care is to provide individuals with point-of-care (POC) CD4 testing at the site of HIV-testing. While this doesn’t remove the linkage step, informing patients of how advanced their infection is has been shown to indirectly improve linkage to care{Larson:2012dy}. Once engaged in pre-ART care, interventions such as decentralising care involving patients switching from hospital-based clinics to primary care centres have been proposed for improving retention{Geng:2010du}. Additionally, POC CD4 testing has also been shown to reduce loss to follow up while patients are engaged in CD4 staging{Jani:2011eb}. Many interventions have additionally targeted retention in ART care, with decentralisation interventions improving care accessibility and reducing loss to follow up{Long:2011cx}. The use of peer health workers to conduct recurrent home-visits, provide counseling and administer a pill count has been shown to reduce the risk of loss to follow up from ART by almost half{Chang:2013ke}. Several reviews have identified multiple interventions to improve ART adherence{Barnighausen:2011cb, Scanlon:2013ko}; including, peer or nurse-delivered directly-observed-therapy (DOT){Pearson:2007fw, Sarna:2008tb}, the use of electronic drug monitoring{Sabin:2010ce}, SMS text message reminders{Lester:2010jp, Mbuagbaw:2014jg}, adherence counseling and education{Chung:2011jm}, together with food incentives{Cantrell:2008ii, Mamlin:2009gf}.

With a variety of interventions aimed at strengthening various points of care, programme providers need to calculate where best to implement interventions to maximise patient outcomes. The concept of the “Cascade of Care” is a means of visualising the events and pathways through care taken by individuals, and allows us to link outcomes to earlier care experience{Kilmarx:2013iy, Hallett:2013ig}. As evidence now highlights deficiencies across the spectrum of care, the traditional concept of linear flow is challenged by trends in the data indicating patients often become lost from care, before subsequently re-engaging, or potentially engage for the first time later than indicated{Hallett:2013ig, Gardner:2011de, Rosen:2011ii}. However, the drivers behind patients’ disengagement and reengagement are still ambiguous; although it has been hypothesised that the development of symptomatic HIV is likely to be key in driving individuals to seek care, data around those lost from care is scarce. To reconcile these trends and to further distinguish the routes into care, we termed the routes by which patients re-engage with care or engage late as “side doors”, to supplement the conventional “front door” route by which care naïve individuals enter{Hallett:2013ig}. Stratifying routes into care in this way allows ART programmes to be properly characterised, enabling insight to be gained from the dynamics of care, which is crucial to understanding where best to intervene and how to prioritise interventions.

To fully characterise care, linked longitudinal data is required at the individual-level to capture the experience of all HIV-infected individuals. Yet the majority of available data is not linked and only describes individuals who have had contact with the clinic. This clinic-level data is biased, as individuals who have never come into contact with the clinic are not accounted for. Additionally, outcomes of patients lost to follow up are also needed to exhaustively characterise care. In summary, these data limitations restrict the ability to which ART programmes can assess themselves and identify where to take action.

However, select facilities in sub-Saharan Africa are beginning to distribute such data, thereby allowing comprehensive insight into the dynamics of care. In this paper, through the use of mathematical modelling, we evaluate an ART-programme in Kenya to demonstrate how to prioritise interventions to improve health outcomes for patients.

# Methods

*Overview*

We constructed an individual-based micro-simulation capturing the care experience of individuals as they progress through an ART programme to evaluate patient outcomes. Initially, we developed a mathematical model describing HIV infection with declining health associated with increased mortality. This natural history model was later expanded to capture the operational steps and milestones that form the structure of an ART-programme using longitudinal data from AMPATH; a consortium in western Kenya established with the aim of creating an HIV care system to assess the outcomes of ART for both rural and urban patients{Kimaiyo:2010tq}.

To assess from where current health losses accrue, the model was calibrated to the setting of western Kenya and the modelled status in care of persons dying from HIV-related causes was estimated. We then explored the impact of a range of interventions, each targeting an aspect of pre-ART or ART care. The impact of each intervention in relation to the baseline scenario indicates the extent to which health outcomes can be improved for patients, along with the cost of these improvements.

## Model description

The natural history model describes infection progression upon HIV acquisition in terms of declining CD4 counts, the development of WHO Stage defining conditions and associated mortality prior to ART initiation. Upon initiating and adhering to ART, CD4 count decline reverses and the individual recovers from their WHO Stage defining conditions. Mortality hazards are associated with each health state, so as ART improves health, mortality rates decrease. However, if an individual fails to adhere to ART, their health declines as if they abstained from treatment.

The model describes the inhabitants of Kenya from 1970 to 2030 and begins by creating a population of HIV-negative individuals the size and age-structure of the observed population in 1970. HIV incidence is informed by estimates from the UNAIDS Spectrum Software{Spectrum:tl}. We begin HIV testing in 2004 and provide ART for eligible individuals. We used the 2004 WHO treatment eligibility guidelines specifying a threshold for treatment of CD4 <200 cells/μl or WHO Stage IV infection{WorldHealthOrganization:2005ws}. This is updated in 2011 to a CD4 of <350 cells/μl or WHO Stage III/IV infection{WorldHealthOrganization:2010wj}. The natural history model was calibrated using surveillance data sourced from the literature. A review was conducted to identify relevant studies that would enable us to calibrate every aspect of the model. Where possible, data from cohort studies was utilised; although, in some situations data from observational studies was used. The full description of each data source used for calibration and detailed methods can be found in the appendix.

The cascade model describes the pathways through care events for HIV-positive individuals (figure 1). Declining health in the natural history model drives care-seeking behaviour in the cascade model; as, when a patient becomes symptomatic (WHO Stage III/IV condition), they seek care at a considerably higher rate than before. HIV-negative care naïve individuals are tested from 2004 onwards by either seeking care (VCT or PICT) or by being actively sought out (HBCT). These routes identify individuals at different places, times and stages of infection, and therefore the impact of testing varies by route. Individuals may be tested multiple times throughout their lives and care will only progress if they are found to be HIV-positive.

To calibrate the cascade model, we utilised a unique high-resolution longitudinal dataset from western Kenya. AMPATH formed in 2001, as a partnership between Moi University, Moi Teaching and Referral Hospital and a consortium of North American academic health centers led by Indiana University working in partnership with the Government of Kenya to utilise the power of universities to enhance care and improve patient outcomes. Additionally, we compared model outputs to national estimates of incidence, prevalence and HIV-related deaths to ensure the model accurately replicated the historical characteristics of the epidemic.



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

## Data

The AMPATH Medical Record System (AMRS) has been collecting individual-level data on the AMPATH AIDS-control system since 2006{Einterz:2007js, Tierney:2007th}. Service delivery occurs through public sector hospitals and health centres run by the Ministry of Health{Einterz:2007js}. Building on well established VCT and PICT programmes, the use of HBCT was trialled in 2007 before becoming a permanent intervention in 2010{Wachira:2013dc}.

Using data from the Port Victoria catchment area, we were provided data on 3,788 HIV-positive individuals followed from 2007 to 2014. Data was collected by combining hospital and clinic databases with patient information from mobile testing teams performing HBCT in the community, using unique patient identification numbers to track patients over time. Working in collaboration with AMPATH, we assessed the proportion of individuals that test through each modality before calculating linkage, CD4 testing and pre-ART retention rates. Where possible these were stratified by current CD4 count and route of entry into care. Among patients initiating ART, we assessed patient retention prior to treatment. Specifically, whether patients had ever been lost from care and if so whether they were eligible for ART when they re-engaged. Additionally, we looked at the number of pre-ART clinic visits and CD4 tests attended prior to ART initiation. Further details of data collected from AMPATH sites can be found in the appendix.

## Cost

To assess the economic impact of care from the perspective of a health care provider, we assigned costs to the individual components of care in the model. The CHAI MATCH Study, a multi-country analysis of 161 treatment facilities across five countries in sub-Saharan Africa provided the annual cost of ART care, the cost of pre-ART clinic visits and CD4 lab-based tests{Tagar:GTMxY-pi}. A review of the literature identified the cost of the remaining aspects of care. Adjustment was made for inflation and location by using the GDP deflator from the International Monetary Fund. All costs are reported in 2013 US$ and were discounted at an annual rate of 6% from 2010 onwards.

## Hypotheses

We hypothesise that current care programmes in Kenya are not performing to their maximum potential, as deficiencies spanning HIV-testing, pre-ART and ART care hinder successful patient outcomes. Therefore, intervening at a single point is likely to have suboptimal impact due to other weaknesses in care and we hypothesise that intervening at multiple points will have a larger impact on care. Additionally, we hypothesise that the full extent of detriment to care is not realised, as current clinic-level data fails to account for individuals who never engage with, or are lost from, care.

## Outcomes

Patient outcomes were quantified as disability-adjusted life-years (DALYs) and evaluated between 2010 and 2030. Disability was weighted according to current HIV-positive health state and ART status, with weights extracted from the Global Burden of Disease Study 2010{Salomon:2012ib}. Financial impact was assessed through quantifying the total cost of care between 2010 and 2030. Additionally, we considered the care experience of patients suffering HIV-related deaths between 2010 and 2030.

## Analyses

To explore the current state of care in Kenya, we assessed patient outcomes between 2010 and 2030 under a baseline scenario. This scenario contained no HBCT, restricting entry to care routes to VCT or PICT, as to be more representative of a typical ART programme in Kenya.

After assessing the current state of care, we explored means of improving patient outcomes through intervening at specific points in care with targeted interventions. We designed twelve interventions that target various aspects of care including an HBCT intervention and a Universal Test & Treat strategy (table 2). Where possible, interventions had two scenarios: “maximum impact” illustrating a maximally effective intervention and a “realistic impact” scenario, demonstrating a more attainable version. To assess the impact of individual interventions, each intervention and scenario was implemented in turn from 2010 onwards and the impact on patient outcomes compared to the baseline scenario to produce outcomes of DALYs averted compared to baseline and the additional cost of care between 2010 and 2030.

To explore the potential impact of multiple interventions each targeting a different point in care, we calculated the cost per DALY averted for each single intervention compared to the baseline scenario and implemented the intervention with the lowest cost per DALY averted. With this first intervention fixed, we assessed the impact of applying a second intervention by simulating the remaining interventions in turn and calculating the cost per DALY averted relative to that of the first intervention, thus identifying the best combination of two interventions with the with the lowest cost per DALY averted relative to a single intervention scenario. This process was repeated to demonstrate the impact of increasing the number of interventions implemented on patient outcomes. Further details of model structure, data collection, calibration and analyses can be found in the appendix while a summary of key assumptions and data sources is shown in table 1.

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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). |  |

Table 1. Key model assumptions and data sources.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Aspect of care to be addressed** | **Intervention type** | **Intervention** | **Maximum Impact** | **Realistic Impact** | **Cost**  **(2013 USD)** |
| Individuals are unaware of their HIV status. At baseline, the mean time for an individual to test through VCT is 7.2 years. Additionally individuals may test through PICT, but the time to test varies depending on 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. 5.4% 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}). |
| Individuals are not connecting to care in timely manner. At baseline, 60% of patients tested through VCT or PICT successfully link to care. | *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*** | 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 engage with care but are subsequently lost prior to starting treatment. On average at baseline, for every CD4 test 56% of patients are lost from care before receiving their results. On the day of a CD4 test result appointment, 20% of patients fail to 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*** | 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 drop out of 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}. |
| Individuals initiate ART but only 75% adhere to treatment. | ***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. 5.4% linked if had not previously been diagnosed, else 25%). | Immediate ART & HBCT (every four years, 90% coverage. 5.4% linked if had not previously been diagnosed, else 25%), but 20% fail to start ART and 20% fail to link to ART | $18 per HBCT person tested ($8 home-visit [*Barnabas unpublished*] + $10 rapid HIV-test{Wright:2004jd}). |

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

# Results

## Current Sources of Health Losses

In our baseline scenario representing the current state of care in Kenya, we observed that among all HIV-related deaths in the community (figure 2, left), the majority (57%) occur in individuals who were diagnosed but failed to start treatment, while 19% of individuals never engaged with care prior to death. The remainder of HIV-related deaths were attributable to individuals who died after initiating ART (24%); with the majority dying after dis-engaging from ART care (12% of all HIV-deaths), 9% dying after initiating ART late (CD4 <200 cells/μl) and the remaining 3% after initiating ART on-time (CD4 >200 cells/μl).

However, if we only consider individuals who came into contact with the clinic (received a CD4 test) and yet suffered an HIV-related death (figure 2, right), the majority of deaths were attributable to those who again were diagnosed but died prior to initiating ART (65%). 17% died after disengaging from ART care, 13% died as a result of the late initiation of ART, and only 5% died after initiating ART on-time. Of all HIV-related deaths seen in the community, 33% were not reported at the clinic as they were among individuals who never engaged with care.

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



## The Impact of Isolated Interventions

We applied each of our 12 interventions in turn and assessed the impact on DALYs averted, compared to baseline, and the additional cost of care, compared to baseline, between 2010 and 2030 (figure 3 and table 3). Universal Test and Treat was found to be the most impactful intervention (5.59m DALYs averted between 2010 and 2030), as this removes pre-ART care completely, initiating all HIV-positive individuals onto ART immediately and actively seeking infected individuals through HBCT. This intervention averts 50% of the DALYs averted if the entire HIV-positive population were placed on treatment immediately from 2010 onwards with perfect adherence and retention to care, representing the maximum attainable impact (MAI). The second most impactful intervention was Immediate ART (3.62m DALYs averted, 32% MAI), followed by HBCT with POC CD4 testing (3.53m DALYs averted, 31% MAI). These three interventions actively seek individuals and in the case of Immediate ART and Universal Test and Treat, remove pre-ART care completely.

The remaining single interventions were less impactful but highlight important issues in the dynamics of HIV care. For instance, the ART Outreach and Adherence interventions were not highly impactful (0.74m and 0.70m DALYs averted, respectively, 6% of MAI) due to upstream weaknesses in care, as many individuals never initiated ART (>75% of all HIV-related deaths between 2010 and 2030).

Among the testing interventions, the maximum impact scenario of HBCT was much more impactful than the VCT intervention (1.88m and 0.62m DALYs averted, 17% and 5% MAI, respectively); however, the HBCT intervention with imperfect linkage to care (realistic scenario), highlights the importance of linkage after HBCT as this was less impactful than the maximum impact VCT intervention (0.43m and 0.62m DALYs averted, 4% and 5% of MAI, respectively). Yet, both scenarios of the HBCT intervention were more than twice as expensive to implement than the VCT intervention ($2.62b, $2.06b and $898.44m (2013 USD), respectively).

Among the linkage interventions, HBCT POC CD4 was the most impactful as it combines HBCT with a POC CD4 test to alert HIV-positive individuals of their eligibility for treatment (3.53m DALYs averted, 31% MAI). This was the second most expensive intervention due to the cost of POC CD4 test kits and the cost of actively seeking individuals at home ($3.13m between 2010 and 2030). Interestingly, the VCT POC CD4 intervention averted more DALYs in the twenty-year period than the Linkage intervention (1.43m vs. 0.82m DALYs averted, 13% vs. 7% of MAI). This is due to the VCT POC CD4 intervention providing perfect linkage to care with the addition of a POC CD4 test; and also explains the difference in cost between the two interventions ($527.20m vs. $294.73m).

Each of the pre-ART retention interventions had a considerable impact on care. Of these interventions, the maximum impact scenario of Improved Care, the intervention preventing any loss from pre-ART care was most impactful (1.95m DALYs averted, 17% MAI), followed closely by the maximum impact scenario of the Pre-ART Outreach intervention that re-engages anyone lost from pre-ART care (1.83m DALYs averted, 16% MAI). Interestingly, the maximum impact Improved Care intervention was only slightly more expensive than the maximum impact Pre-ART Outreach intervention; this was due to the cost of additional testing that retaining individuals in pre-ART care incurs ($983.26m vs. $689.03m). Comparing the POC CD4 intervention against the VCT POC CD4 intervention, the former was less impactful and also cheaper than the latter (1.35m DALYs averted, 12% MAI, at a cost of $498.27m vs. 1.43m DALYs averted, 13% MAI, at a cost of $527.20m). The reasoning behind this is that the VCT POC CD4 intervention immediately links all individuals testing through VCT and provides them with a POC CD4 test; whereas, the POC CD4 intervention applies only to individuals who have entered pre-ART care. That is, patients that have successfully linked to care. Thus, without perfect linkage POC CD4 involves testing fewer individuals. Furthermore, the ART retention interventions were constrained by the limited number of individuals whom initiated ART. Nonetheless, both scenarios of the ART Outreach intervention had a larger impact and were more expensive (by increasing the total life-years spent on ART) than the adherence interventions.

## The Impact of Bundles of Interventions

An optimal combination of interventions can be found by simulating all possible combinations and selecting those that, at each budget level, provide the greatest increase in health. We did this for all the ‘realistic’ interventions 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 3).

A combination of six interventions averts 4.45m DALYs (39% of MAI) at a cost of $353 per DALY averted. The interventions used are ART Outreach, POC CD4, VCT POC CD4, Linkage, Pre-ART Outreach and Adherence (table 3). This combination of strengthening linkage, pre-ART retention and ART retention, greatly improved care and reduced the total DALYs accrued by HIV-positive individuals.

Comparing the cost and impact of a combination of interventions, with the results of the univariate analysis (figure 3), the combination of interventions produces 88% of the impact of the realistic Universal Test and Treat intervention (4.45m vs. 5.08m DALYs averted, 39% vs. 45% of MAI) at 44% of the cost per DALY averted ($353 vs. $803 per DALY averted), shown in table 3 illustrating ICERs as the incremental cost per DALY averted by a combination of interventions compared to the previous combination and ACERs as the total cost per DALY averted compared to the baseline scenario.

The total number of HIV-related deaths between 2010 and 2030 for the combination of interventions was substantially lower than at baseline (913,256 vs. 1,466,458 deaths, respectively), and was comparable to that of Universal Test and Treat (913,256 vs. 907,011 respectively); however, the distribution of care experience between the two strategies differed(figure 4). With the combination of interventions, the majority of HIV-related deaths occurred among individuals who had not initiated ART, with 24% of individuals never tested and 33% of individuals diagnosed but never initiated ART. Yet, this is a reduction from the baseline scenario where 57% of HIV-related deaths were among individuals who were tested but never initiated ART. In contrast, HIV-related deaths when the Universal Test and Treat intervention was applied were predominantly among patients who had initiated ART (87%), and in particular those who initiated ART but were then lost from care (51%).

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

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

# Discussion

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



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.