Evaluating Strategies to Improve HIV Care Outcomes in Western Kenya

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# Abstract (300 words)

## Background:

With pressure on donor governments and multilateral organisations to reduce HIV funding to recipient countries, the effectiveness of current HIV programmes is brought into question. Evidence suggests that in many instances ART-programmes in sub-Saharan Africa are not maximally effective. Patients ~~make inadequate use of HIV clinic facilities~~, are often lost from care and initiate treatment late, leading to suboptimal treatment outcomes. We aimed to assess the state of a current ART-programme in western Kenya and the potential for interventions to improve treatment outcomes for patients.

## Methods & Findings:

We constructed an individual-based mathematical model to describe cohorts of HIV infected adults experiencing HIV care in an ART-programme in western Kenya. The model simulates natural HIV progression and mortality through CD4 cell count stages and clinical symptoms. We calibrated the model to a high-resolution longitudinal dataset from The Academic Model for Providing Access To Healthcare (AMPATH) describing the dynamics of patient flow through care. We explored the impact of 12 interventions on care to understand where care was suboptimal and could be improved. We assessed health outcomes in terms of disability-adjusted life years (DALYs) averted and additional cost relative to baseline. Our results indicate that in western Kenya, the effectiveness of current ART-programmes can be improved. While interventions targeting HIV testing and pre-ART retention are highly impactful (averting 3.5m and 1.9m DALYs between 2010 and 2030, respectively), losses from care occur throughout leading to suboptimal treatment outcomes for patients. A combination of interventions targeting multiple points of care is more cost-effective than implementing a single intervention such as Universal Test and Treat ($353 vs. $803 per DALY averted, respectively).

## Conclusions:

Our results suggest that ART-programmes in western Kenya can be enhanced to bring about greater health benefits. In this setting, the most cost-effective way to strengthen care is through a combination of interventions targeting multiple points of care.

# Introduction (*1000 words*)

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 sparse{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}. This value of pre-ART retention was further broken down to indicate that 59% of patients were retained from HIV testing to receipt of CD4 test results, whereupon 46% of remaining individuals were retained until they were eligible for ART and finally 68% of the remainder were retained until they initiated ART{Rosen:2011ii}. While among those patients initiating ART, recent estimates from South Africa indicate that 81% are 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 more 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 that 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 due to care-fatigue, 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 as opposed to having to 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}. 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 collect and distribute this type of 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 *(500 words)*

*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 acting at various points along the care pathway. 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 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 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.

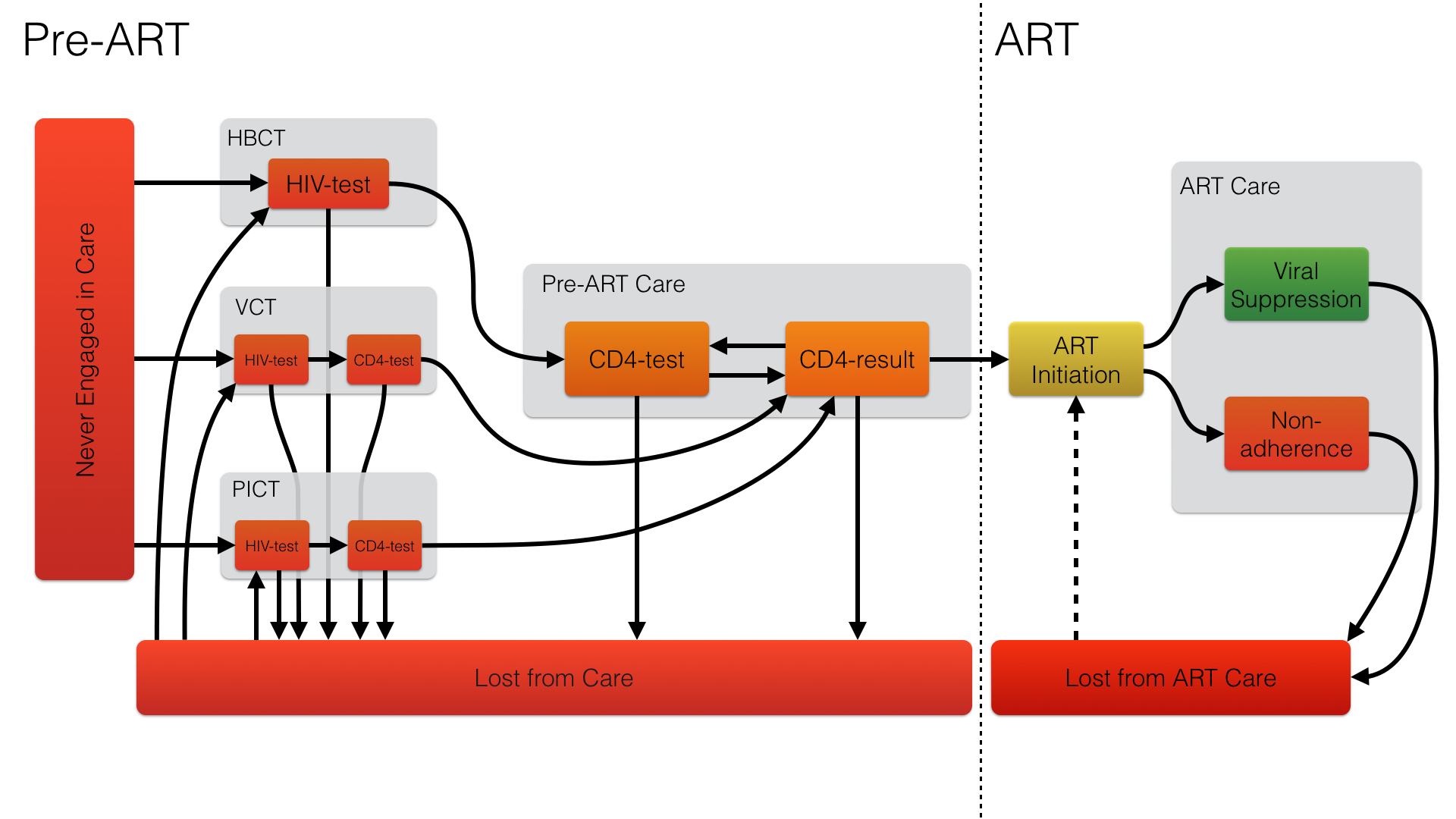


Figure 1. Flow diagram representing the operational steps involved in navigating an ART-programme.

## 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 trialed 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 initially 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 were eligible for ART when they re-engaged with care. 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 of 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 targetted interventions. We designed twelve interventions that target various aspects of care including an HBCT intervention and a Universal Test & Treat strategy (table 1). Where possible, interventions have 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 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 targetting a different point in care, we calculated the cost per DALY averted by a single intervention, over 20 years, compared to the baseline scenario and implemented the most cost-effective intervention (with the lowest cost per DALY averted). With the most cost-effective single intervention fixed, we then calculated the most cost-effective combination of two interventions compared to the baseline scenario. This process was repeated to demonstrate the impact of increasing the number of interventions implemented on patient outcomes in comparison to a single intervention. Further details of model structure, data collection, calibration and analyses can be found in the appendix.

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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 in the literature. |
| 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). |  |

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| **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 1. Summary of interventions applied from 2010 to 2030.

# Results *(1000 words)*

*Current Sources of Health Losses.*

We ran the model in the absence of any interventions to define a baseline scenario. At baseline, the only route into the HIV care system is via testing through VCT or PICT.

We assessed the outcomes of patients from the viewpoint of the clinic and the community. The view of the clinic, considers the care experience of all individuals initiating ART; whereas, the community view considers the care experience of all individuals who suffered an HIV-related death regardless of their state of engagement with care. From figure 2, if we look from the viewpoint of the clinic, where we examine the history of care engagement among individuals initiating ART between 2010 and 2030, we see that 44% of patients that engage with the clinic are retained until they initiate ART. However, 41% of the deceased persons were eligible at first contact with the clinic and are initiated onto ART immediately. Among deceased persons that had engaged with pre-ART care, are lost to follow-up but subsequently re-engage with care, <1% are not eligible for treatment at return to pre-ART care.

In contrast, from the perspective of the whole community, we see that the majority of HIV-related deaths (57%) are from individuals who were diagnosed but failed to start treatment. Among the <24% of individuals that initiated ART, the majority died after disengaging from ART care, with the remainder dying as a result of the late initiation of ART (with a CD4 count at initiation of <200 cells/µl) and only a very small proportion dying after initiating ART on-time.

Figure 2. Comparison between the community view and the clinic view of HIV Care.



*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). Universal Test and Treat is by far the most impactful intervention (5,587,234 DALYs averted between 2010 and 2030), as this intervention does away with pre-ART care completely, initiating all HIV-positive individuals onto ART immediately and actively seeking infected individuals through HBCT. The second most impactful intervention is Immediate ART (3,616,936 DALYs averted), followed by HBCT with POC CD4 testing (3,534,967 DALYs averted). 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 are less impactful but highlight important issues in the dynamics of HIV care. For instance, the ART Outreach and Adherence interventions are not highly impactful (744,915 and 697,265 DALYs averted, respectively) due to weaknesses in care upstream, many individuals never initiate ART (>75% of all HIV-related deaths between 2010 and 2030).

Among the testing interventions, the maximum impact scenario of HBCT is much more impactful than the VCT intervention (1,882,403 and 615,857 DALYs averted, respectively); however, the realistic scenario of the HBCT intervention (imperfect linkage to care) highlights the importance of linkage after HBCT as this is less impactful than the maximum impact VCT intervention (431,574 and 615,857 DALYs averted, respectively). Yet, both scenarios of the HBCT intervention are 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 is the most impactful as it combines HBCT with a POC CD4 test to alert HIV-positive individuals of their eligibility for treatment (3,534,967 DALYs averted). This is 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 averts more DALYs in the twenty-year period than the Linkage intervention (1,434,508 vs. 815,994 DALYs averted). This is due to the VCT POC CD4 intervention providing perfect linkage to care with the addition of a POC CD4 test; this also explains the difference in cost between the two interventions ($527.20m vs. $294.73m).

The pre-ART retention interventions each have quite an impact on averting DALYs. Of these interventions, the maximum impact scenario of Improved Care, the intervention preventing loss from pre-ART care was most impactful (1,949,321 DALYs averted), followed closely by the maximum impact scenario of the Pre-ART Outreach intervention that re-engages anyone lost from pre-ART care (1,825,372 DALYs averted). Interestingly, the maximum impact Improved Care intervention is only slightly more expensive than the maximum impact Pre-ART Outreach intervention; this is due to the cost of additional testing retaining individuals in pre-ART care incurs ($983.26m vs. $689.03m). If we compare the POC CD4 intervention against the VCT POC CD4 intervention, we see that the former is less impactful and also cheaper than the latter (1,352,379 DALYs averted at a cost of $498.27m vs. 1,434,508 DALYs averted 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 testing involves testing fewer individuals. As previously mentioned, the ART retention interventions are not quite so impactful as few individuals ever initiate ART. However, both scenarios of the ART Outreach intervention are more impactful and more expensive (by increasing the total life-years spent on ART) than the adherence interventions.

*The Impact of Bundles Of Interventions*

Our results from the univariate analysis indicate that there is no single high-impact low-cost intervention, highlighting that there is no single point of weakness along the cascade of care but rather deficiencies throughout. An optimal combination of interventions can be found by simulating all possible combinations of interventions 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 has been included in the combination at one budget level it cannot be removed at higher budget levels. Figure 4.

A combination of six interventions averts 4.45m DALYs at a cost of $353 per DALY averted. The interventions used are ART Outreach ($310 per DALY averted), POC CD4 ($346 per DALY averted), VCT POC CD4 ($347 per DALY averted), Linkage ($348 per DALY averted), Pre-ART Outreach ($351 per DALY averted) and Adherence ($353 per DALY averted). These interventions, strengthening linkage, pre-ART retention and ART retention, greatly improve care and reduce the total DALYs accrued by HIV-positive individuals.

If we compare the cost and impact of our combination of interventions (table 2), with the results of our univariate analysis (figure 3), we see that our combination of interventions produces 88% of the impact of the realistic Universal Test and Treat intervention (4,450,326 vs. 5,078,370 DALYs averted) at 44% of the cost per DALY averted ($363 vs. $803 per DALY averted), shown in figure 4.

While the total number of HIV-related deaths between 2010 and 2030 for the combination of interventions is comparable to that of Universal Test and Treat (91,326 vs. 90,701 respectively), the distribution of care experience among patients who suffer HIV-related deaths differs (figure 5). With the combination of interventions, the majority of HIV-related deaths occur among individuals who have not initiated ART, with 24% of individuals never tested and 33% of individuals tested but never initiating ART. Yet, this is a dramatic 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 is applied are predominantly among patients who have initiated ART, and in particular those who initiated ART but were then lost from care (51%).

**Thought:**

*In the intro I talk about what we SEE (late entry to care, low CD4 at ART) and how the reason WHY is due to deficiencies in care. And therefore we must INTERVENE.*

*Can I come full circle and say that at baseline, with deficiencies in modelled care, we SEE the SAME characteristics of patients entering care (late / lost / low / die)??*



Figure 3. Cost-effectiveness of individual interventions impacting on HIV care.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Intervention | DALYs averted (*D*) | Additional Cost  (2013 USD) (*C*) | ICER  *(C1-C2) / (D1-D2)* | ACER  *C / D* |
| ART Outreach | 629,616 | $194,921,903 | 309.59 | 309.59 |
| ART Outreach +  POC CD4 | 2,223,066 | $769,432,754 | 360.55 | 346.11 |
| ART Outreach +  POC CD4 +  VCT POC CD4 | 2,912,715 | $1,012,525,439 | 352.49 | 347.62 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage | 3,176,865 | $1,104,688,485 | 348.90 | 347.73 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach | 3,589,899 | $1,261,612,686 | 379.93 | 351.43 |
| ART Outreach +  POC CD4 +  VCT POC CD4 +  Linkage +  Pre-ART Outreach +  Adherence | 4,450,327 | $1,571,236,159 | 359.85 | 353.06 |



Figure 4. Cost-effectiveness of multiple interventions impacting on HIV care overlaid on top of fig. 3.

Table 2. Cost-effectiveness of implementing a combination of interventions impacting on HIV care.

# 



Figure 5. Care experience of deceased individuals who suffered an HIV-related death between 2010 and 2030. Also referred to as the viewpoint of the community in figure 2.

# Discussion *(1500 words)*

Here’s a “body plan” for the Discussion…

Para 1: Summarise your findings – deaths from outside clinic setting, no single bullet interventions, combinations good that attack all parts of the cascade, potentilaly gets as great an impact as UTT, although “immediate ART” gets almost same impact and is a lot simpler.

These results show that within an ART programme in Kenya and under our baseline conditions care is suboptimal. Whilst the clinic’s viewpoint indicates that nearly half of all individuals initiating ART were successfully retained in pre-ART care, this outlook fails to capture individuals who never engaged with care. When viewed from outside a clinic setting, the majority of HIV-related deaths are 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 ART (figure 2). Intervening at various points in care with our individual interventions has illustrated that HIV-testing and pre-ART retention are particular weak points in care, as interventions targeting them, such as HBCT or Improved Care, are highly impactful (figure 3). In contrast, removing pre-ART care all together (Immediate ART) and additionally actively seeking individuals (Universal Test & Treat) averts the most DALYs between 2010 and 2030; however, these interventions are expensive to implement. From our analysis of these individual interventions, no single large-impact low-cost intervention was identified. The high impact interventions are expensive, with a high cost per DALY averted and vice versa; yet the majority of interventions tested fell into the category of small-impact low-cost. We identified a combination of six interventions that when applied simultaneously improve patient outcomes at a cost of $353 per DALY averted (in comparison to baseline). This combination strengthens care at multiple points and is potentially as impactful as the Universal Test and Treat intervention but with a lower average cost-effectiveness ratio. However, a cheaper alternative in the form of an Immediate ART intervention may be simpler to implement and yet still be highly impactful.

Para 2: So what should the world do based on this? Stop looking at outcomes from only clinic perspective, but evaluate from poplation perspective. Look at deaths in the community. Understand point in the cascade for persons dying. Stop focussing on and evaluating single interventions. Don’t roll-out a wide-spread UTT until the cascade is fixed. See Immediate ART for what it is – a way to circumnavigate operational challeneges (and secondarily, to get prevention impact) rather than as a way to gain additiaonl clinic benefit.

This work indicates that it is imperative for ART programmes to evaluate patient outcomes from the population perspective. The viewpoint of the clinic 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, deaths in the community must also be considered. 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 implementing interventions to improve care, many current interventions only target one aspect of care{Kilmarx:2013iy, Barnighausen:2011cb,Govindasamy:2014fa}. Therefore, the desired impact of any 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 capped by downstream losses from pre-ART and ART care. Thus, care must be systematically strengthened to fully realise the benefits afforded by ART. Importantly, interventions utilising an immediate ART strategy circumnavigate the operational challenges of pre-ART care by removing it, potentially depriving patients of its ancillary benefits{Burtle:2012kw,Govindasamy:2014fa}. This type of intervention does not target care at the clinic level but avoids the problem to reap the prevention benefit.

Para 3: Say it isn’t exactly AMPATH, but is a bit like W Kenya and maybe elsewhere. Talk about difference between settings. Talk about other model results.

This model was predominantly calibrated using a longitudinal dataset provided by AMPATH of western Kenya. However, only the elements of HIV care were calibrated to the 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, little insight is currently available as to the state of care in other sub-Saharan countries. 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. Indeed, in our model, this type of intervention becomes much more powerful if upstream care is made perfect[*results not shown (in LeaksReverse.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}.

With interest in characterising and quantifying the HIV cascade peaking in recent years, there still exists a need for comprehensive individual-level longitudinal data. Cross-sectional studies are only able to provide a static snapshot of the situation. Yet, to gain insight into the changing dynamics of care over time and to identify where best to intervene, longitudinal data is required. AMPATH is one of the few groups in sub-Saharan Africa able to provide such high-resolution data{Tierney:2007th}, but it is hoped that as the use of mobile technology for data collection increases, a clearer image of the state of care in sub-Saharan Africa will begin to emerge.

Para 4: Talk about how there is a big difference between “interventions” that can have the same name, and that this is a caraciture. Case in point is the HBCT of AMPATH vs that of Connie/Ruanne/Jennny.

While this work discusses individual interventions by name, there are often big differences between interventions of the same name{Barnighausen:2011cb}. For example, in the case of HBCT interventions, two such interventions have been trialled in different locations in sub-Saharan Africa with dramatically differing results. An intense HBCT intervention was tested in Kwazulu-Natal between 2011 and 2012 involving home-based HIV-testing followed by immediate POC CD4 testing and later by follow-up visits to facilitate linkage to 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 between 2009 and 2011 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 POC CD4 testing and including follow-up visits to motivate individuals to link; however, while these interventions are often collectively referred to as HBCT, they are very different in structure and hence produce variable results. [ *does this mention the chimeric nature of HBCT* ]

Go through the results again, this time slower and drawing in comparison to other data.

1. Deaths outside clinic. Reference the ALPHA stuff.
2. Intervention bundles (tiering reference)
3. Immediate ART – Lots of people saying this is sensible. ALso is in sympathy with (UNPUBLISHED UNTIL FEB 2015) findings from Rosen et al about how same-day ART gets more people suppressed. (granich?)

Considering the distribution of care experience among individuals who suffered an HIV-related death between 2010 and 2030 (figure 2), 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 and indicates that the majority of mortality is occurring outside the clinic.

Additionally, we illustrated that no single low-cost high-impact intervention currently exists, but that the most cost-effective pathway for improving care involves a combination of six interventions including: ART Outreach, POC CD4, VCT POC CD4, Linkage, Pre-ART Outreach and Adherence (figure 4). This combination of six interventions is highly cost-effective in comparison to the Universal Test and Treat intervention, averting 88% of the DALYs averted by the Universal Test and Treat intervention at 44% of the cost per DALY averted. 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 interventions. These two interventions are the most impactful, but fail to address any deficiencies downstream of ART initiation, resulting in patients being lost from care or failing to achieve viral suppression. 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. Confidential. Unpublished*]. The idea of “Test and Treat”, a strategy involving initiating all infected individuals onto ART once identified has gained significant traction in recent years{Granich:2009hv,Walensky:2002ve,

Eaton:2013bv}. In part due to the hypothesis that initiating ART early would reduce transmission and therefore reduce the future ART need{Eaton:2012bk}. While the impact of ART in reducing transmission is undeniable{Cohen:2011kr}, the major benefit of immediate ART from our model results, in terms of patient outcomes, is brought about by avoiding loss from care and keeping people healthy and suppressed on ART.

Interestingly, comparing the distribution of care experience among deceased individuals when the combination of interventions is implemented to Universal Test & Treat highlights how both strategies significantly reduce HIV mortality but that this is achieved through different methods (figure 5). We see that the combination of interventions is 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%) being lost from ART care before death. Therefore, the total person-time spent on ART by individuals in the Universal Test & Treat intervention exceeds that of individuals in the combination intervention scenario, this is reflected by the increased cost of the Universal Test & Treat intervention and the larger proportion of cost that is attributable to ART care.

Big Finish: Tell me about the future: We don’t know about motivations of patients (that’s important), We don’t know how this plays out in other settings. We don’t know how intervengtions put together would work. And we haven’t got a clue about costs in reality.

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 of cost, but the true scalability of these costs and their representation of the cost of intervention execution are debatable.

Knock-out Blow: Nevertheless, we feel this analysis will powerfully SHAPE the discourse around the cascade and inteventions that are formulated, evaluated and rolled-out to improve the impact of programs.

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.

The tools used to fight HIV are becoming more akin to those used to treat a long-term chronic disease{vanSighem:2010gw}. Identifying infected individuals is no longer the biggest hurdle, but rather obtaining and retaining viral suppression in patients on ART for their entire lives has emerged as the next major challenge. This modelling exercise aims to explore an ART-programme and understand where potential exists to improve care and patient outcomes using western Kenya as our setting.

Our baseline scenario is representative of the current state of an ART-programme in western Kenya in the absence of any major intervention (such as HBCT). The two viewpoints in figure 2 describe almost contrasting stories. As far as the clinic can see, the majority of patients are retained in care successfully until ART initiation or initiate as they enter care, leading to only a small number of individuals engaging, disengaging and then re-engaging with pre-ART care. While this sounds promising, the viewpoint of the clinic is biased; only individuals who have contact with a clinic are accounted for. However, stepping back to consider the community’s viewpoint, we observe a much more harrowing story. In reality, and obscured from the view of the clinic, the majority of HIV-related deaths between 2010 and 2030 are due to patients who were diagnosed, but owing to the suboptimal state of the HIV-care system in western Kenya, never initiated treatment (57%). *[Ideally want to make a comparison to Andrew and Valentina’s work here (the pies from the cascade workshop), this work hasn’t been published though. Additionally, Dan Klein’s pie charts from his presentation that would make a good comparison (SA / Zimbabwe)]*.

Additionally, nearly 20% of individuals’ who suffer an HIV-related death, die unaware of their infection. Of the ~24% of individuals who did initiate ART but subsequently suffered an HIV-related death, the majority of these individuals died after being lost from ART care, with the remainder dying while on ART. While both viewpoints are informative, the community’s perspective highlights the weaknesses in care that lead to individuals losing life-years to HIV.

Using our range of 12 interventions to study how patient outcomes can be improved, we see that individual interventions have varying levels of success (figure 3). These interventions illustrate the impact of improving a single point of care along the cascade. While removing pre-ART care altogether, such as in the Universal Test and Treat and Immediate ART interventions, is highly impactful (averting 5,078,370 and 3,616,936 DALYs, respectively), these interventions are not the most cost-effective solution.

An impactful intervention, one that averts DALYs, highlights a weak point in care that can be strengthened. For example, the home-based counselling and testing interventions (HBCT and HBCT POC CD4), both actively seek out individuals at home for testing. These interventions have a large impact on care, averting 1,882,403 and 3,534,967 DALYs respectively, which signifies that patients are seeking care inadequately. However, diagnosis is not the only barrier to HIV care, patients must then successfully link to care and receive a CD4 test. The HBCT interventions rely on two rates of linkage to care: (1) linkage given that the patients was unaware of their infection prior to the current visit and (2) linkage given the patient was previously diagnosed and aware of their infection. This distinction allows individuals who were previously diagnosed to link to care at faster rate than individuals who have just learned of their infection.

Aside from HBCT, the three interventions that target pre-ART retention (Pre-ART Outreach, Improved Care and POC CD4) are also particularly impactful, indicating that retaining patients in pre-ART care is suboptimal and can be improved upon. Surprisingly, the ART Outreach intervention has little impact on care, averting only 744,915 DALYs, but this is due to the small proportion of individuals that ever initiate ART (<20% of all PLWHIV on ART). This result contrasts to findings from a modelling study conducted by Klein *et al.* (2014), in which they found that improving the re-initiation of ART in a treatment programme in South Africa was a highly cost-effective intervention{Klein:2014ho}. The model of South Africa was calibrated to UNAIDS Spectrum estimates of the number of people on ART over time, something that this model doesn’t quite match, leading us to speculate that a larger proportion of individuals initiated ART in the Klein model and therefore an intervention such ART Outreach would have a larger impact than in the results presented here. In another mathematical model of HIV testing strategies in South Africa, Bendavid *et al*. demonstrated 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 the results presented here, further illustrating the importance of successfully linking patients to care{Bendavid:2010gu}.

Overall from the analysis of these individual interventions, there is no single large-impact low-cost intervention. The high impact interventions are very expensive, with a high cost per DALY averted and vice versa. The majority of interventions tested fall into the category of small-impact low-cost.

With many current interventions only targeting one aspect of care{Kilmarx:2013iy, Barnighausen:2011cb,Govindasamy:2014fa}, their impact 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. In the model this is highlighted by the ~20% of individuals who die before being diagnosed with HIV (figure 2). Therefore, a combination of interventions targeting multiple points in care may be a more cost-effective solution than a single point-intervention.

Our results indicate that while many possible intervention combinations exist, for this particular setting, the most cost-effective pathway for improving care is as follows: ART Outreach, POC CD4, VCT POC CD4, Linkage, Pre-ART Outreach and Adherence (figure 4). This combination of six interventions is highly cost-effective in comparison to the Universal Test and Treat intervention, averting 88% of the DALYs averted by the Universal Test and Treat intervention (realistic scenario), at 44% of the cost per DALY averted. This indicates that intervening at multiple points to strengthen care is almost as effective as removing pre-ART care in its entirety. Additionally, the ancillary benefits of pre-ART care must not be overlooked as patients retained in pre-ART care will be counselled, receive treatment for opportunistic infections and also may receive psychological support{Burtle:2012kw,Govindasamy:2014fa}. *[Ideally like to make a comparison to Andrew and Valentina’s expansion pathway presented at the cascade workshop here, presuming this is confidential until published though]*

Therefore, our model results show that a combination of interventions is key to maximising health benefits while still being cost-effective in comparison to single intervention. However, interventions impacting the entire spectrum of care maybe equally beneficial. It has recently been hypothesised that tiered care, using patient strata to determine the provision of different care services, is likely to improve patient outcomes whilst reducing costs *[Struggling for a reference here, aside from Chris Duncombe’s forthcoming “Overview of optimised models of care delivery for HIV”]*.

An example of this type of intervention comes from Babigumira *et al.* (2011), in which a task-shifting intervention was implemented for eligible patients at an HIV clinic in Kampala, Uganda{Babigumira:2011gg}. Eligibility criteria selected adherent, healthy 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. Another example of tiered care illustrates how decentralising adherent patients on ART from a hospital-based clinic to a primary health care facility managed by nurses reduced the annual cost of care by 11% without compromising patient outcomes{Long:2011cx}. However, as this was an observational study, patients were not randomised to the down-referral group and as such this may have introduced undesirable bias into the results.

Nevertheless, these tiering interventions raise an important issue regarding the current characterisation of the cascade of care. That is, whether the stages constituting the cascade differ between populations. For instance, pregnant women are now likely to be diagnosed with HIV at an antenatal clinic where they will then receive treatment immediately, regardless of CD4 count, continuing for life{WorldHealthOrganization:2013we}. Therefore, for these individuals many of the stages defined as part of the care continuum are absent. In other key populations, such as female sex workers, physical or social barriers may be present preventing access to certain stages of care. For example, female sex workers are likely to be wary attending clinic appointments and disclosing their serostatus for fear of stigmatism and loss of business{Mountain:2014da}. Thus, tiering interventions allow for the fragmentation of care into different populations to account for these differences. Perhaps alluding to multiple variants of the cascade.

With interest in characterising and quantifying the HIV cascade peaking in recent years, there still exists a need for comprehensive individual-level longitudinal data. Cross-sectional studies are only able to provide a static snapshot of the situation. Yet, to gain insight into the changing dynamics of care over time and to identify where best to intervene, longitudinal data is required. AMPATH is one of the few groups in sub-Saharan Africa able to provide such high-resolution data{Tierney:2007th}, but it is hoped that as the use of mobile technology for data collection increases, a clearer image of the state of care in sub-Saharan Africa will begin to emerge.

Among the strengths of this work, the model accurately captures the natural history of HIV infection and replicates the epidemic from 1970 onwards matching incidence and prevalence estimates from UNAIDS and the Kenya AIDS Indicator Surveys from 2007 and 2012. The model has been calibrated to a high-resolution data set describing an ART-programme in western Kenya and is able to reproduce key patterns of flow through HIV care along with the distributions of individuals seeking care. The interventions applied to the model are based on real-world interventions and the model is able to capture their direct effects, through averting DALYs and reducing mortality, along with indirect effects from reducing onward transmission.

However, these results are only relevant to one particular ART-programme in western Kenya and while several key outputs are comparable to national estimates, the generalisability of the results to the rest of Kenya or even sub-Saharan Africa remain open to debate. However, these results provide insight into the likely situation of many ART-programmes in resource-limited countries. Future research in different locations will help to provide a more accurate picture of the state of ART-programmes in sub-Saharan Africa.

Additionally, assumptions were made in the model regarding the drivers behind care seeking behaviour as very little data exist on what causes infected individuals to seek care. For example, in the model the rates at which individuals seek care depends upon a combination of their previous care experience and their current health status. When a patient is diagnosed with HIV, they seek care at a higher rate than when they were oblivious to their infection. Also, after receiving the results of a CD4 test, where a patient learns how advanced their infection is, they seek care at a higher rate still. Upon developing symptomatic HIV, characterised by having a WHO Stage of III or IV, patients seek care very quickly. We feel as though these subtle distinctions in treatment seeking behaviour are sensible estimates for use in this model. While more research is required, the interplay between patient behaviour, economic factors and the availability of health services, and their roles in determining a individual’s propensity to seek and be retained in care has already been alluded to{Burns:2014jz}.

The interventions examined in this study are all rooted in scientific literature and have the potential to be implemented. The two scenarios for each intervention, maximum impact and realistic impact, were designed to illustrate the hypothetical maximum impact that an individual could obtain together with a more feasible scenario. Costs were applied to interventions were possible but it should be noted that additional costs are likely to be incurred when implementing certain interventions. The interventions modelled are applied from 2010 onwards and take immediate effect. In reality, interventions are likely to be scaled up over time and in the case of implementing multiple interventions; these may be rolled out at different time points. While the model has the ability to explore these scenarios it is beyond the scope of this paper. While it must be stressed that the cost-effectiveness of the interventions described are relevant for this particular ART-programme in sub-Saharan Africa only, the model can easily be re-calibrated to another setting provided the data exist for an accurate calibration. For a given budget, interventions could be adjusted to assess the best possible use of funding.

This work utilises an almost unique dataset to assess the current state of an ART-programme in western Kenya. Through the use of a mathematical model, we are able to understand where care is currently suboptimal. Then by implementing a range of interventions acting on various points of care, we highlight strategies that strengthen care, leading to improved patient outcomes through reducing DALYs, mortality and HIV incidence. As with strengthened care, the benefits afforded by ART can be fully realised as treatment programmes become more effective.

Future research can build on these results in two ways. Firstly, by assessing the current weaknesses in other ART-programmes in sub-Saharan Africa we will be able to develop a clearer image of the state of HIV care across the continent. This is, however, highly dependent upon detailed longitudinal datasets becoming available, but will provide insight into the interventions best suited to be implemented in different settings. Secondly, upon implementing interventions in western Kenya, the results of the model can be validated. While it will be difficult to assess some output metrics, a comparison between the viewpoint from the clinic on the ground and the results of the model could be particularly useful for assessing the impact of an intervention.

As donor organisations constrict funding for HIV programmes in Kenya and the government struggles to fill the void, attention must turn to increasing the efficiency of currently implemented programmes to deliver treatment in a cost-effective and sustainable framework. Our results indicate that in western Kenya, the effectiveness of current ART-programmes can be improved. While interventions targeting HIV testing and pre-ART retention are highly impactful, losses from care occur 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 the most cost-effective way to strengthen current ART-programmes. Optimising care will improve patient outcomes directly by increasing ART coverage, diminishing community viral load and reducing life-years lost to HIV, and also indirectly by reducing HIV incidence.

# Acknowledgements

# References

# Figure Legends

*Figure 1 – Model representation of the cascade of care*

*Figure 2 – Comparison between the community view and the clinic view of HIV care*

*Figure 3 – Cost-effectiveness of individual interventions impacting on HIV care*

*Figure 4 – Cost-effectiveness of implementing multiple interventions impacting on HIV care*

*Figure 5 – Cost-effectiveness of multiple interventions impacting on HIV care overlaid on top of fig. 3*

*Table 1 – Summary of interventions applied from 2010 to 2030.*

# Supporting Information

See appendix.

***Notes***

1. Previously, Outreach interventions had a cost of $469 per person returned to care. Simon Walker advised me that this cost would likely not scale well. I’ve since revised this to $19.55 per person sought (value comes from the same paper).

*I compared the cost of the outreach interventions using the old ($469) and the new ($19.55) costs. Results in link below:*

<https://drive.google.com/file/d/0B02uVauBTUwhUHQzUURtUnZiMFk/view?usp=sharing>

1. Should I include all the data that AMPATH has provided us in the Appendix?
2. Should I include a table with all the parameter values for the model?
3. Are we publishing the code along side this?
4. I deviated slightly from the plan for assessing the impact of a combination of interventions. We had discussed explaining exploring two scenarios:
   1. How to improve health outcomes within current budget framework / redistribution of costs.
   2. How to maximally improve health outcomes with a large budget increase e.g. $10m. [*figure 4*].

I haven’t done this yet as we never discussed it further than an idea for the paper. Not sure if this is still the direction we are pursuing. Also, I wasn’t sure where to get the current budget for treatment in Kenya / AMPATH from and how to divvy it up across interventions.

1. I’m thinking that the layout of figure 3 may need adjusting, regarding the positioning of the table etc. Also figure 4 / 5 may need to be altered / merged / re-formatted.
2. ***jjo11:cascade:CareCascadeV2:December:15th:Normal:plots:propMaxDalyImpact.pdfAdditional figure idea:*** If we put people immediately onto ART as soon as they get infected (from 2010) and put everyone with HIV on ART in 2010 with zero dropout and perfect adherence… what kind of DALYs do we accrue? A maximum value that we could potentially hit. ***25,306,171 DALYs between 2010 and 2030.*** The figure below illustrates the proportion of this “maximum possible” value that each intervention averts.

***Main question the paper answers:***

1. *How should we prioritise interventions? (what order)*
2. *Is a single intervention sufficient? ( single / combination )*
3. *What are the caveats?*

***Three main messages of the paper:***

1. *No single point of weakness in care (care is suboptimal throughout)*
2. *Combination of interventions is as effective but cheaper than UTT (yet mortality distribution differs (fig. 5))*
3. *Not generalisable to SSA, we need more data. This work will shape future intervention decisions…*