Evaluating Strategies to Improve HIV Care Outcomes in Western Kenya

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# Abstract

## Background:

## Methods & Findings:

## Conclusions:

# 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 9 million people are receiving ART in sub-Saharan Africa{UNAIDS:2014ta}. With proper adherence, treatment can increase life-expectancy such that it approaches that of an HIV-negative individual{Nakagawa:2013cv}. Therefore, we might expect that with access to ART, the life-expectancy of HIV-positive individuals would increase dramatically; yet this does not appear to be the case, with life-years still being lost to HIV in this thunderous epidemic{Collaboration:2008ed}. Additionally, patients are initiating ART late with CD4 counts far lower than current treatment guidelines recommend (102 cells/μl at treatment initiation reported in South Africa between 2001 and 2009, when guidelines recommend initiation when CD4 decreases below 200 cells/μl{Boulle:2014uj}), highlighting the potential failures of pre-ART care{Boulle:2014uj}. The consequences of late treatment initiation are grave for both the infected individual and others that they may have transmitted the virus to, resulting in suboptimal treatment outcomes. The meagre performance of these HIV care systems has caught the attention of donors organisations, where budget constraints are forcing a shift in focus towards maximising the effectiveness of current ART-programmes[[UNAIDS Gap Report 2014](http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf)].

Accumulating evidence suggests that HIV care is suboptimal not at one particular point, but across all stages of ART-programmes, as “cascading losses” have been reported throughout care{Rosen:2011ii}. However, this issue is not just confined to sub-Saharan Africa; substantial losses in care have also been reported in highly developed countries too{Nachega:2014ks}. In 2011, a systematic review by Rosen and Fox illustrated that, in sub-Saharan Africa, the median proportion of patients retained from HIV testing to receipt of CD4 test results was just 59%. Of the individuals that received CD4 test results, 46% were retained until they were eligible for ART, and finally of those retained until they were eligible for ART, 68% were retained until they initiated ART. This review marked the first time that losses across the whole of pre-ART care had been quantified on a large scale. Previous studies assessing ART care in Mozambique illustrated that, 43.5% of patients were lost between HIV-testing and enrolling in pre-ART care. Of those that did enroll in pre-ART care, 22.9% were lost before receiving CD4 testing and of those who were found to be eligible for ART, 68.7% failed to initiate ART{Micek:2009hs}. Addressing why patients disengage from care, together with identifying means of returning them will improve patient outcomes by allowing for the on-time initiation of ART and retention in ART care.

Visualising the events and pathways taken by individuals through care is important step in understanding where losses are occurring and how to prevent them. Often termed, the “Cascade of Care”, this conceptualisation of an ART-programme allows us to assess patient outcomes and assign blame to events in time{Kilmarx:2013iy, Hallett:2013ig}. The Cascade of Care begins with the identification of HIV-positive individuals through HIV-testing. This involves the patient seeking care voluntarily at a voluntary counselling and testing clinic (VCT), or in a healthcare setting through provider-initiated counselling and testing (PICT). Alternatively, the patient may be sought by a home-based counselling and testing team (HBCT) and diagnosed in their home. Alerting individuals to their HIV-status is still a challenge in sub-Saharan Africa, with current estimates showing only 45% of people living with HIV are aware of their status{UNAIDS:2014ta}. Kenya has made progress towards its goal of 80% awareness of HIV status, with 72% achieved in 2007{NASCOP:2012tp}. However, the marginal opportunity cost of identifying individuals increases substantially as the pool of undiagnosed HIV-positive individuals decreases. Additionally, gaining insight into the drivers behind care-seeking behaviour may help inform future HIV-testing strategies{Moses:1994tg}.

Once diagnosed, individuals need to be linked to pre-ART care; meaning they must attend a clinic to be bled for a CD4 test in order to determine their eligibility for ART. Kranzer *et al.* define linkage to HIV care as attending for a CD4 count measurement within six months of diagnosis to assess ART eligibility{Kranzer:2010hp}. In this study, they found that among 885 individuals tested between 2004 and 2009 in Cape Town, South Africa, 37.4% failed to link to care{Kranzer:2010hp}.

After successful linkage to care, where the patient is bled for an initial CD4 count, the patient must return at a later date to receive the results of the test. This is due to CD4 tests in sub-Saharan Africa being predominantly lab-based, where the sample must be processed centrally, with a turn around time of up to two weeks{Larson:2012dq}. In resource-limited settings travelling to the HIV clinic is expensive and may involve individuals having to take a day off work to travel from remote areas, resulting in a decreased salary{Geng:2010fh}. A study by Larson *et al*. (2010) found that among individuals who received CD4 tests at a clinic in Johannesburg, South Africa, and were not immediately eligible for ART, 65% failed to return to receive the results of their CD4 test within 12 weeks{Larson:2010dz}. Unfortunately, insights into the role of care seeking behaviour are currently relatively limited; unlike in tuberculosis (TB) research where several studies have attempted to identify the drivers behind health care seeking behaviour{Buregyeya:2011fi, Salaniponi:2000tc, Pronyk:2001uk}. However, the distance and cost associated with travelling to an HIV-clinic have already been cited as motives to disengage from care{Geng:2010fh, Yu:2007wh, Ware:2009id}. In many cases, pre-ART care can be rather prolonged, with the patient enduring multiple CD4 tests and clinic visits prior to ART initiation. This can lead to care-fatigue, where patients disengage with care as they are not receiving any therapeutic benefit. This is backed up by findings from Kenya, in which a CD4 count of >200 cells/μl at enrollment into pre-ART care was shown to result in a 3.49 fold increase in the odds of being lost from care{Geng:2010du}.

Eligibility for treatment is determined by country-specific guidelines. The latest guidelines published by the World Health Organization released for adoption in June 2013 state ART should be initiated when a patient’s CD4 count drops below 500 cells/μl{WorldHealthOrganization:2013we}. After receiving confirmatory CD4 test results determining ART eligibility, patients must undergo counselling before initiating ART. In some settings, owing to the significant losses occurring upstream in pre-ART care, only 18% of tested individuals have been shown to be successfully retained in care until ART initiation{Rosen:2011ii}. Additionally, multiple large scale studies have shown that CD4 counts of patients initiating ART to be far lower than recommended treatment guideline values at the time{Nash:2011ki, Boulle:2014uj}; therefore, indicating pre-ART care, in many settings, to be poor at retaining healthy individuals until they become eligible for treatment.

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, in sub-Saharan Africa between 46-85% of patients are retained 24 months after initiation{Rosen:2007hd}. One study of over 200 thousand individuals across sub-Saharan Africa showed ART retention fell each year on treatment (77.4% at 12 months, 75% at 24 months, and 70.5% at 36 months), with attrition averaging 5% per year after 24 months, highlighting long-term retention on ART as an obstacle to achieving optimal patient outcomes in resource-limited settings{Fox:2010gt}.

Substantial evidence now highlights deficiencies in both pre-ART and ART care, challenging the traditional concept of linear flow through the cascade, in which patients move sequentially between events. The reported structural failures and discrepancies of current ART-programmes therefore suggest that care is perhaps more cyclical than linear; with this “churn” of patients engaging and disengaging over time{Gill:2009dj, Hallett:2013ig, Miller:2014ba}. If patients’ initiate ART late, with very low CD4 counts, after being lost from care, the route back into care becomes an important target for interventions. We [*I had originally said Hallett & Eaton, but perhaps it should say we?]* termed these re-engagement routes as “side doors” into care, to supplement the traditional “front door” route into care through which care naïve individuals enter{Hallett:2013ig}. This “side door” distinguishes patients with no previous care experience from those reconnecting with care, thus allowing us to understand the different dynamics of these two routes into care. Gaining insight into how these patients lost from care re-engage, and how care-naïve individuals engage for the first time is vitally important in terms of repairing and reinforcing care.

However, the drivers behind patients’ disengagement and reengagement are ambiguous, and while it has been hypothesised that the development of symptomatic HIV is likely to be key in pushing individuals to seek care, data on individuals lost from care is scarce. Currently available clinic-level data highlights the need for a consistent definition of “lost to follow-up”, together with the need for high-resolution longitudinal data that will enable us to map the individual pathways taken by patients through care. A potential drawback of clinic-level data is the perspective of the clinic, which can only provide details of individuals who have engaged with care. There are likely to be many HIV-positive individuals in the community who fail to seek or be engaged in care, indicating that clinic-level data may be failing to realise the scope of the issue.

Fortunately, a select few facilities in sub-Saharan Africa are beginning to collect and distribute this type of data, thereby allowing us to disentangle the web of routes through care and accurately calibrate mathematical models to provide insight into the dynamics of the cascade of care. In this paper we evaluate an ART-programme in western Kenya. Through the use of mathematical modelling, we identify weaknesses resulting in suboptimal patient outcomes and demonstrate how interventions targeting different points of care can improve health outcomes for patients.

# Methods *(500 words)*

*Overview*

We constructed an individual-based micro-simulation to capture the experience of individuals as they move through the various stages of HIV care. The first step involved developing a mathematical model that described the progression of HIV infection with declining health status and associated mortality. This HIV Natural History model was then expanded to capture the events that make up an ART-programme, the so-called HIV Cascade of Care.

The Natural History model was calibrated using surveillance data from the literature to accurately describe HIV progression and mortality prior to ART initiation, followed by immunoreconstitution after ART initiation. Calibrating the flow of individuals through HIV care in the cascade model was undertaken by utilising high resolution longitudinal data from AMPATH in western Kenya, thus allowing us to model the current state of this specific ART-programme. To understand how costs accrue in an ART-programme, data was sought that described the cost of the individual components of care (e.g. Rapid HIV-test or pre-ART clinic appointment).

To assess where care is suboptimal in this specific ART-programme in western Kenya, the calibrated model was used to replicate the HIV epidemic together with the scale up of treatment from 2004 onwards. Output metrics are DALYs averted and cost between 2010 and 2030. In the absence of any interventions, we were able to define baseline values for impact and cost. 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 mathematical model we constructed can be described as two sub-models: The Natural History Model and The Cascade Model. These two models work to describe the health status of an HIV-positive individual and their movements through care.

The Natural History Model is described in more detail in the appendix but briefly, we model 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, the mortality hazard decreases. However, if an individual fails to adhere to ART, their health declines as if they were not on ART.

The model describes the population of Kenya from 1970 to 2030 and begins by creating a cohort of HIV-negative individuals the size and age of the population in 1970. Population growth is captured through the birth of new individuals over time. HIV incidence is driven by estimates from the UNAIDS Spectrum Software (developed by the Futures Institute[[link](http://www.unaids.org/en/dataanalysis/datatools/spectrumepp2013/)]) before being distributed and randomised to individuals in specific age and sex categories informed by incidence rate ratios also extracted from Spectrum. We start HIV testing in 2004 along with rolling out ART for eligible individuals. We used the 2004 WHO Treatment Eligibility Guidelines of a CD4 count <200 or WHO Stage IV {WorldHealthOrganization:2005ws}. This is updated in 2011 to a CD4 count of <350 or WHO Stage III/IV{WorldHealthOrganization:2010wj}.

The Cascade Model, shown in figure 1, describes the events and pathways through care for HIV-positive individuals. Declining health in The Natural History Model drives care-seeking behaviour in the Cascade Model. As described above, the model begins with HIV-negative care naïve individuals. Individuals are then tested from 2004 onwards through one of three routes: HBCT where individuals are sought and tested at home, VCT where individuals voluntarily attend an HIV-clinic or PICT where individuals seek care due to being symptomatic or having had previous healthcare experience. If an individual is found to be HIV-negative, they do not progress any further through care. They may be tested multiple times throughout their lives and care will only progress if they are found to be HIV-positive. The model is described in detail in the appendix.

## Natural History Calibration



Figure 1. Model Representation of the Cascade of Care

The Natural History Model was calibrated using surveillance data sourced from the literature. A review of the literature was conducted to identify relevant studies that would enable us to calibrate every aspect of the Natural History 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.

## Cascade of Care Calibration

To calibrate the Cascade Model describing the experience of HIV-positive individuals as they move through the various stages of HIV care, we utilised a unique high-resolution longitudinal dataset from western Kenya. The Academic Model for Providing Access To Healthcare (AMPATH), based in Eldoret, is made up of 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.

Since launching in 2006, the AMPATH Medical Record System (AMRS) has been collecting individual-level data on the AMPATH AIDS-control system, which has been described as a model of sustainable development{Einterz:2007js, Tierney:2007th}. Service delivery occurs through public sector hospitals and health centers run by the Ministry of Health{Einterz:2007js}. AMPATH has very well established VCT and PICT programmes, and after trailing the use of HBCT in 2007, officially rolled it out in 2010{Wachira:2013dc}. Recently, AMPATH is extending this with their Find-Link-Treat-Retain programme (FLTR); involving finding all HIV-infected individuals, linking each to care, treating them with ART and retaining them in care for life)[[website](http://news.medicine.iu.edu/releases/2014/05/ampath-abbvie-hiv-testing.shtml)].

AMPATH’s ability to look back at the care history of individual patients, through tracing their unique identification number allowed us to ask very specific questions regarding the flow of individuals through care. Using data from the Port Victoria catchment area, data analysts at AMPATH calculated the losses occurring at each stage of HIV care from 2007 to June 2014, and together with the average delay between each event we were able to extract parameter values that were directly inputted into the model, together with calibration points such as the distribution of CD4 counts at ART initiation. Calibration was undertaken systematically to ensure we were accurate in capturing the changing dynamics of care. Full details of the Cascade Model calibration can be found in the appendix.

## Cost Derivation

The cost of the individual components of care was included in the model. The majority of costs, including the cost of ART care, pre-ART clinic visits and CD4 lab-based tests, were derived from the CHAI MATCH Study, a multi-country analysis of 161 treatment facilities across five countries in sub-Saharan Africa[[MATCH](http://thedata.harvard.edu/dvn/dv/chaighf/faces/study/StudyPage.xhtml?studyId=85882&tab=catalog)]. The remaining costs were sourced from the literature. All costs were adjusted for inflation and location by using the gross domestic product deflator from the International Monetary Fund. Including the cost of the individual components of care in the model allows us to understand how costs accrue and compare in an ART-programme. Additionally, when interventions are applied, we can see the financial implications of improving care. Further details of the breakdown of cost in the model can be found in the appendix.

## Output Metrics

The output metrics from the model were DALYs averted and cost accrued between 2010 and 2030. We weighted DALYs according to current HIV-positive health state and ART status using weights from the Global Burden of Disease Study 2010{Salomon:2012ib}. We also looked at the care experience of individuals who died from HIV-related deaths between 2010 and 2030. Further details can be found in the appendix.

## Assessing Losses in Care

To assess the current state of our specific ART-programme in western Kenya, we assessed the total number of DALYs and cost of care that accrue between 2010 and 2030. This was conducted in the absence of HBCT, so the only means of entering care was through VCT or PICT. HBCT was removed as home-based counselling and testing is not currently found in most ART-programmes in sub-Saharan Africa, therefore providing a more representative baseline scenario.

The care experience of individuals who died from HIV-related deaths was also studied in the baseline scenario to identify, for example, the proportion of individuals who never seek care prior to dying from HIV. This can be thought of as the “view” from the community. It allows us to consider all HIV-positive individuals and their personal experience of care prior to an HIV-related death. This is easy to quantify in the model, but it is more difficult to accurately assess cause-specific mortality in the field. Additionally, the care experienced by individuals who suffer HIV-related deaths is likely to be significantly altered by interventions aimed at strengthening care. Therefore, we also consider the “view” from the clinic, looking at the care experience of all individuals initiating ART. It allows us to understand from the clinics perspective the experience of patients who have engaged with care. This can easily be measured by an ART clinic to assess the current state of practice. The impact of interventions aimed at improving care can also be measured by assessing changes from both the community’s and the clinic’s perspective. For example, the model can calculate the impact of an intervention and if the intervention were then to be rolled out, a clinic would be able to validate the intervention against the model output.

The differences between these two viewpoints are important for assessing the current state of an ART-programme. From the clinic’s perspective, an individual’s first contact with the clinic is to receive either an HIV-test or to be bled for their initial CD4 count. The clinic can easily trace patients from this point onwards. However, the clinic is unaware of HIV-positive individuals that never seek care. Thus, the community’s viewpoint allows us to look at the larger denominator of all HIV-positive individuals and their experience of care.

## Intervention Development

To further understand where care in western Kenya is suboptimal, we designed 12 interventions targeting various points throughout HIV-care. Each intervention is summarised in table 1 and detailed in full in the appendix. Where possible, each intervention has two scenarios: a “maximum impact” scenario illustrating the best possible impact of the intervention and a “realistic impact” scenario, which aims to demonstrate the impact of a more obtainable intervention. Interventions were implemented in the model from 2010 onwards and their impact on DALYs averted, costs accrued and the care experience of individuals dying from HIV-related deaths quantified.

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| --- | --- | --- | --- | --- |
| **Intervention type** | **Intervention** | **Maximum Impact** | **Realistic Impact** | **Cost**  **(2013 USD)** |
| *Testing* | ***HBCT*** | Every four years, 90% coverage of population. 100% linked to care. | Every four years, 90% coverage. 5.4% linked if never diagnosed, else 25%. | $18 per HBCT person tested. |
| ***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. |
| *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. |
| ***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. |
| *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. |
| ***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 bleeding and result are instantaneous. | | $70 per POC CD4 test. |
| *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. |
| ***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. |
| *Sweeping Changes* | ***Immediate ART*** | No pre-ART care, all individuals who enter care are treated immediately. | | No additional costs applied. |
| ***Universal Test & Treat*** | Immediate ART & HBCT | Immediate ART & HBCT, but 20% fail to start ART and 20% fail to link to ART | $18 per HBCT person tested. |

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

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# Results *(1000 words)*

To assess the current state of ART-programmes in western Kenya, 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.

After simulating the population of Kenya from 1970 to 2030 and replicating the HIV epidemic, we assessed the outcomes of patients from the viewpoint the clinic and the community. As can be seen from figure 2, if we look from the viewpoint of the “clinic”, where we consider the engagement of individuals with the clinic prior to ART initiation between 2010 and 2030, we see that 44.33% of patients that engage with the clinic are retained until they initiate ART. However, 41.20% of patients are eligible at first contact with the clinic and are initiated onto ART immediately. Among patients that engage with pre-ART care, are lost to follow-up but subsequently re-engage with care, only <1% are not eligible for treatment at return to pre-ART care.

Looking at the care history of all HIV-positive individuals who died from an HIV-related death between 2010 and 2030 from the “community” perspective, we see that the majority of HIV-related deaths (57.11%) are from individuals who were diagnosed but failed to start treatment. Nearly 20% of individuals in the community were never even diagnosed as HIV-positive before suffering an HIV-related death. 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.

To gain further insight into the state of current ART-programmes in western Kenya and understand where care is suboptimal, 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). From a univariate analysis of the interventions, if we consider only the impact of each intervention on averting DALYs between 2010 and 2030 (x-axis, figure 3), we see that 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 are large scale hard hitting interventions that actively seek individuals and in the case of Immediate ART and Universal Test and Treat, remove pre-ART care completely. The remaining interventions are less impactful but highlight important issues in the dynamics of HIV care. For instance, the ART Outreach and Adherence interventions are not particularly 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).

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



Working through the interventions in groups, the maximum impact scenario of HBCT is much more impactful than the VCT intervention (1,882,403 and 615,857 DALYs averted, respecitvely); 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, indicating that they are remedying a weakness in care. 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 likely 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 POC CD4 intervention is less impactful and also cheaper than the VCT POC CD4 intervention (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.



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

After investigating the impact of individual interventions on reducing life-years lost to HIV, we looked at multiple combinations 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. Therefore, a combination of interventions improving care at multiple points may prove to be cost-effective.

We began by assessing the results of the univariate analysis (figure 3) to find the most cost-effective intervention; that is to say the intervention with the lowest cost per DALY averted. For these analyses we only focused on the realistic scenario of interventions. The most cost-effective individual intervention was ART Outreach ($310 per DALY averted). To understand how a combination of interventions could be utilised to improve care, we applied the ART Outreach intervention at baseline and simulated the effect running each of the remaining interventions in turn to assess the most cost-effective combination of two interventions. A combination of ART Outreach and POC CD4 interventions was found to be most cost-effective ($346 per DALY averted). We repeated this process multiple times to identify an expansion pathway of interventions improving care (figure 4). The most cost-effective combination of six interventions averts DALYs at a cost of $353 per DALY averted (2013 USD). 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, improve 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 (figure 4), 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 5.

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



Figure 5. Cost-effectiveness of multiple interventions impacting on HIV care overlaid ontop of figure 3.

# Discussion *(1500 words)*

As we progress through the fourth decade of this tenacious epidemic, 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.

***Baseline***

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 (57.11%). *[Ideally want to make a comparison to Andrew and Valentinas 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)]*.

A further cause for concern is the nearly 20% of individuals who 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.

***Univariate***

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. This has been informed by data from AMPATH.

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.

***Multivariate***

With many current interventions only targeting one aspect of care{Kilmarx:2013iy, Barnighausen:2011cb,Govindasamy:2014fa}, the 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 more cost-effective 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, 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 maybe 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.

* **Strengths**

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.

* **Limitations**

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 role in determining a person's propensity to seek and be retained in care has already been alluded to{Burns:2014jz}.

* **Clinical relevance**

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.

* **Key implications of this research**
  + Weaknesses exist in this specific ART-programme in western Kenya.
  + Current funding for ART could be more impactful if these weaknesses in care were addressed and resolved.
  + Multiple interventions acting on various aspects of care are likely to be more effective than a single intervention.
  + Tiering interventions?
* **Generalisability**
  + This research only focuses on one location so the results are not generalisable to the entirety of sub-Saharan Africa.
  + However, these results provide some insight into the likely situation of many ART-programmes.
  + Future research in different locations will allow for interventions to be tailored for a specific site, and also to provide a more up to date picture of the state of ART-programmes in sub-Saharan Africa.
* **How can future research build on these observations**
  + AMPATH are highly unique in having collected a large database from many sources that has the ability to link patients from various stages of care. This has allowed them to track an individual patient over time from initial diagnosis through the various events that make up HIV-care.
  + The ability to track patients over time is key, more studies are required reporting this type of data.
  + This will allow us to track population health over time, as well as assess the impact of interventions that may be being rolled out.
  + Future research can identify losses in care in other locations in SSA, together with identifying whether a different set of interventions may be more impactful in another location.
  + Future research may also test the impact of the interventions suggested in this location to further validate the model results.
* **Future work**
  + Calibration of model to a new location.
  + Comparison between two or more locations.
  + Detailed investigation into role of health care seeking behaviour.
  + Assessing the value of the proposed WHO “monitoring and evaluation” indicators.

***Final paragraph***

In this setting, our results show that a combination of interventions targeting multiple points of care is most cost-effective than any individual intervention.

*“Treatment deliver must conducted in a cost-effective and sustainable framework” – me*

Optimising care will improve patient outcomes directly by increasing ART coverage and diminishing community viral load, and indirectly by reducing HIV incidence.

Prevention? Prevention continuum? {McNairy:2014dk}

# Acknowledgements

# References

# Figure Legends

*Figure 1 - Flow diagram of the cascade of care*

*Figure 2 - Status quo scenario from the perspectives of the clinic and the community*

*Figure 3 - Cost Impact plot illustrating the cost and impact of various interventions*

*Figure 4 - Combination of approaches for improving health outcomes for patients*

*Table 1 - Summary of interventions acting on the cascade of care*

# Supporting Information

**THOUGHTS**

*Potential things to include in introduction:*

* The interplay between patient behaviour, economic factors and the availability of health services plays an important role in determining a person's propensity to seek and be retained in care{Burns:2014jz}.
* This “cascade” of losses across all stages of HIV-care means that the benefits afforded by ART are not fully realised.
* Clinic vs. community
* The widespread scale-up of HIV-testing during the last decade together with the increased availability of treatment has shifted bottlenecks in care away from the availability of testing and treatment to the logistics and organisation of HIV care.
* With renewed focus on cutting costs and funding constraints on large donors, existing HIV care programmes must be strengthened to improve the cost-effectiveness of treatment.
* WHO Guide and Tools for programme managers to collect data on Cascade [[link](http://applications.emro.who.int/dsaf/EMROPUB_2014_EN_1639.pdf)]
* Inclusion of Jain et al. (2014) paper on ART delivery among asymptomatic people initiating with CD4 >350 cells. [Not randomized and likely only treatment-KEEN people].

*🡪 Clinic level programmatic measures of success (if the intervention is successful, what will the clinic see? Increase in throughput? More drug stockouts? Higher CD4 at entry to care / ART initiation?) [this will be useful for the figure 2 narrative. [perhaps place this in results]*

***Additional Figure Ideas***

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.

***jjo11:cascade:CareCascadeV2:December:15th:Normal:plots:propMaxDalyImpact.pdf***