

Priorities for HIV Care in Sub-Saharan Africa: A Population Perspective

The HIV Modelling Consortium.

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1. Executive Summary

The provision of antiretroviral therapy (ART) has dramatically reduced HIV-related mortality in generalised HIV epidemic settings. However, over a decade since the introduction of ART, mortality rates among HIV positive adults remain three to six times higher than those not infected with HIV.

Understanding the HIV care experience, if any, among persons dying from HIV are crucial for identifying gaps in HIV care and providing direction for programs to improve, but direct population-wide data on this are sparse in high-prevalence HIV epidemic settings. In this report, we consult empirical data and mathematical modelling to estimate and project the relationship of the HIV care experience and mortality among people living with HIV.

Addressing the “When to start ART” question, we use models to simulate the potential impact of immediate ART initiation (irrespective of CD4 cell count) on HIV mortality and transmission.

Key Conclusions on the Care Cascade:

- Based on empirical data and model inference, in generalised epidemic settings, the majority of HIV-related deaths occur among adults who are **never engaged** with or **disengaged** from the HIV care system at the time of death.
- In settings with mature ART programmes presently, between **45% and 60% of all HIV-related deaths** are estimated to occur among adults who have initiated ART. Mortality rates are highest among persons on ART 6 months or less—indicative of **late initiation**—and those who have **disengaged or experienced gaps in ART care**.
- Over the coming decade, an estimated **15–35% of HIV deaths** in the will occur among **adults never linked to care**, assuming current patterns of HIV testing and linkage continue.
- Focusing on improvements in patient monitoring and care for those on **ART for at least six months** could only affect a relatively **smaller proportion (10–30%) of deaths** occurring among patients who are stable on ART.
- **Persons disengaged** from ART (following ART initiation) have a **very high mortality rate**. The contribution of this group to overall HIV-related deaths is projected to **increase** in the coming decade and amount to **20–35% of HIV-related deaths** if current levels of disengagement and return to care persist.
- Clinic-based indicators derived from outcomes of patients who enter care is insufficient for evaluating the overall effectiveness of HIV care and treatment programmes.

- Population level data, particularly population surveillance of deaths, would help to decrease uncertainty in model-based inferences.

Key Conclusions on ‘When to Start’:

- Poor retention in pre-ART care results in **missed opportunities** to initiate patients onto ART, who are subsequently lost and may return to care too late or not at all. **Immediate ART initiation** for all patients linking to HIV care is predicted to result in **6–14% fewer HIV-related deaths over the next decade than there would be if ART initiation policy remained as is**. The vast majority of that impact is due to this strategy initiating more people on ART in a timely manner rather any direct therapeutic or prevention benefits conferred by a change in eligibility from the current guidelines.

2. Introduction

Antiretroviral therapy (ART) has substantially reduced HIV-related mortality in generalised HIV epidemic settings in sub-Saharan Africa. Over the decade since ART has been available, the life expectancy for all adults has increased by around ten years in general population cohorts under demographic surveillance in eastern and southern Africa (Reniers *et al* CROI 2015). However, HIV-positive adults still experience 3 to 6-times higher mortality rates compared to those who are not infected with HIV in settings with mature HIV programmes (Reniers *et al*. AIDS 2014). Understanding the sources and reasons for excess HIV-related mortality in settings where ART is available is essential for prioritising interventions towards the points in the HIV care and treatment system where this remaining HIV-related morbidity and mortality can be reduced most effectively.

This report describes which stages of HIV care give rise to the greatest share of HIV-related deaths based on observational studies that link mortality among HIV-positive adults to previous HIV care and treatment experience and mathematical modelling. We used mathematical modelling to project how the distribution of mortality across care stages will evolve in the future and evaluate the effects on mortality of one potential modification in ART programmes - to change the eligibility criteria for ART initiation so ART initiation is immediate and does not require a CD4 count

3. Empirical evidence from mortality surveillance

Directly observed information about the previous HIV care experience among adults suffering HIV-related mortality are sparse due to limited availability of vital registration and other mortality surveillance in generalised HIV epidemic settings.

We rely on two data sources to review empirical estimates of the HIV care experience among persons dying from HIV in settings with mature ART programmes in sub-Saharan Africa:

- General population cohort studies among populations under demographic and HIV surveillance in the ALPHA network, and
- Individually linked vital registration and HIV care and treatment data from the Western Cape, South Africa.

General population cohort studies from the ALPHA Network

The ALPHA Network (<http://alpha.lshtm.ac.uk/>) consists of general population cohort studies in which a geographically defined population is under routine demographic surveillance—

recording all births, deaths, and migrations in the population—and regular home-based population-wide HIV serosurveillance. Some sites are able to link demographic and HIV surveillance information to patient data from local HIV care and treatment facilities, furnishing population-wide estimates of HIV prevalence, mortality among HIV-negative and HIV-positive adults, and by stages of HIV care. Analysis for this report consists of data from four of these cohort studies (Table 3.1, Figure 3.1).

Table 3.1: ALPHA network sites included in this analysis

Study site	Country	Adults (15+ y) under surveillance, 2013	Dates of HIV surveillance	HIV prevalence at last sero-survey	% of HIV positive ever started ART, 2012
Rakai	Uganda	20,055	1998-2012	11%	28%
Masaka	Uganda	9,697	1989-2014	10%	26%
Karonga	Malawi	18,580	2007-2012	6%	41%
uMkhanyakude	S. Africa	39,145	2003-2014	28%	41%

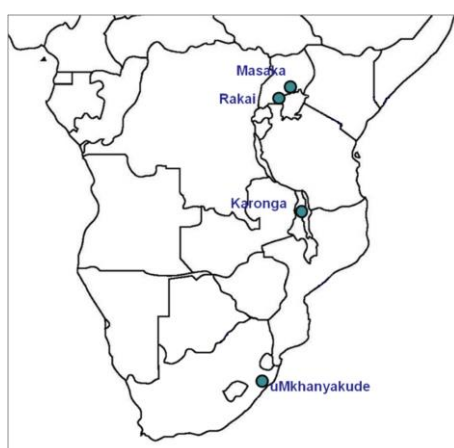


Figure 3.1: Locations of the ALPHA Network general population cohort study sites included in this report.

The mortality rate among HIV-positive adults has declined dramatically in all sites since the availability of ART and continued to decline as programmes have matured (Figure 3.2). In each site, the 2011–'12 mortality rate among HIV-positive adults was around 25 per 1000 PYs, a 3 to 4 fold reduction from peak mortality levels. Deaths among adults on ART have increased as a proportion of all deaths in HIV-positive adults, but in 2012 the majority of deaths occurred among adults who had not initiated ART, except uMkhanyakude, in KwaZulu-Natal, South Africa, where about 40% of deaths to people living with HIV occurred in adults who had never initiated ART, 20% in those who had recently initiated, and 40% amongst those having initiated more than six months ago.

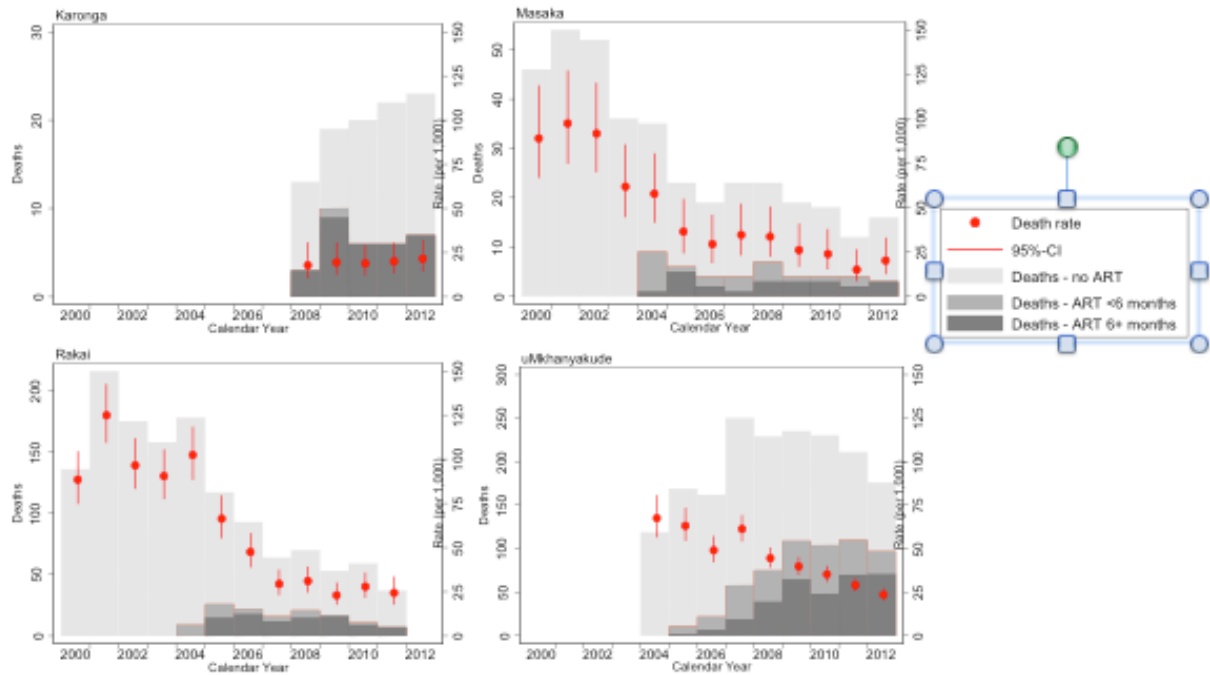


Figure 3.2: Mortality rates among HIV-positive (red dots and 95% CIs), and the number of deaths to known HIV-positive adults by ART experience.

Figure 3.3 stratifies the mortality analysis by the main stages of HIV care. Excess HIV mortality rate is calculated as the difference in mortality between HIV-positive adults compared to HIV-negative counterparts in the same five-year age group. HIV-related mortality rates are highest among adults on ART less than six months and among those who have disengaged from ART care or experienced gaps in receiving HIV treatment. However, these stages represent the smallest proportion of the HIV-positive population in 2009-2012, and so the contribution of these stages to total HIV deaths is relatively small at this time.

The largest proportion of the population is in the ART naïve groups, and mortality among each of these groups—undiagnosed, diagnosed and not in care, and linked to care—is considerably higher than mortality among patients stable on ART for greater than six months. As such, patients not yet on ART still contribute the majority of excess HIV deaths in most sites.

Figure 3.3B summarizes the distribution of excess HIV-related deaths across the care stages in each of the four sites. In most sites, the largest share of HIV-related deaths occur among patients who are not yet in care or undiagnosed—between 20 and 50% of HIV-related deaths.

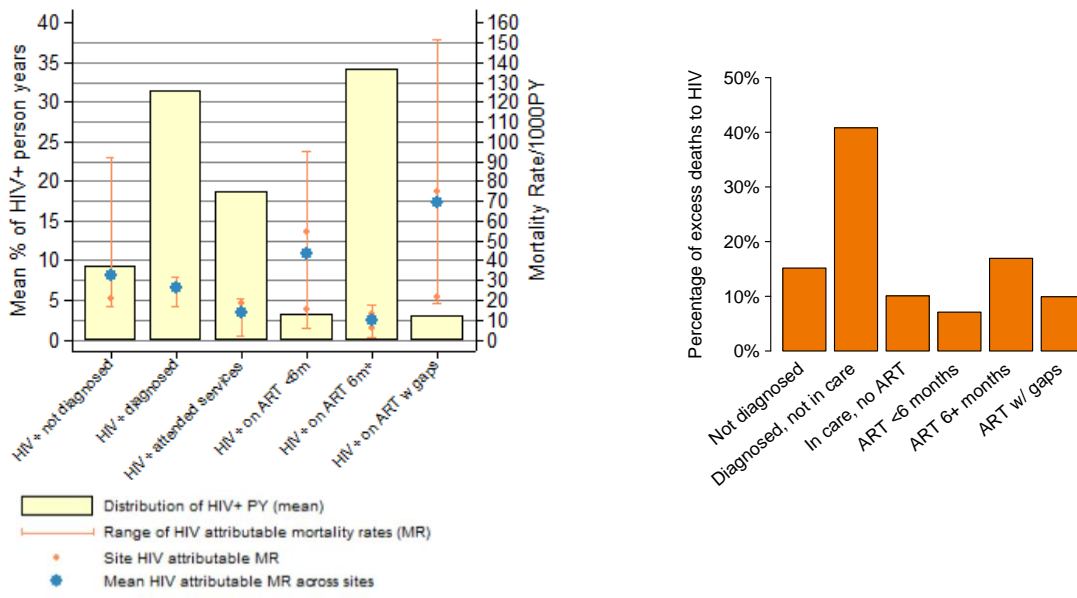


Figure 3.3: HIV-related mortality across stages of care in ALPHA Network sites. (A; left) Distribution of the population in each stage of HIV care (bar height; left axis) and excess HIV mortality rate (blue dots; right axis). (B; right) Distribution of excess deaths across care stages, combining excess mortality rate and person-years in each stage. Data pooled over all sites for period 2009 through 2012 or 2013.

Linked vital registration and HIV care and treatment in Western Cape, South Africa

Boulle and colleagues retrospectively linked HIV-associated adult deaths recorded in the Western Cape vital registration system in 2012 to patient records from HIV care and treatment (Boulle et al. 2014). A total of 38,695 adult deaths were recorded in 2012, of which 3370 were recorded as HIV-associated. Of these, 3161 (94%) were linkable to a unique patient identifier in the medical record system.

Table 3.2 summarise the stage of care reached for the 3161 HIV positive deceased persons. Eight hundred (25%) had no evidence of previous HIV-related care, 1118 (35%) had a CD4 count test but never started ART, and 1243 (39%) had previously been on ART. Among those with a CD4 count, but had never initiating ART, 882 (79%) had a CD4 count below 350 cells/ μ L and were eligible for ART under guidelines in force at that time, but did not initiate.

Among those patients who did initiate ART, 312 deaths (34%) occurred among those who had been on ART less than 6 months, indicative of late ART initiation attributable to failure of earlier diagnosis and linkage to care. A further 628 deaths occurred among patients who had last received ART more than 6 months before death (326 deaths) or experience a gap in treatment of 3 months or more. Only 303 deaths (9.6%) occurred among patients who had continuously been in care for the previous year—focusing on improvements to care for patients continuously on ART could only have averted a maximum of around 10% of HIV-related deaths in this year.

Table 3.2: Previous HIV care experience among HIV-related adult deaths in Western Cape, 2012.

HIV care experience	Deaths	Percentage
Not diagnosed or not linked to care	800	25.3%
Linked to care, never initiated ART	1,118	35.3%
On ART <6 months	312	9.9%
Lost from ART care or >3 month gap in receiving ART in the past year	628	19.9%
On ART continuously for >6 months	303	9.6%
Total	3,161	100%

4. Mathematical models

To supplement directly observed data about previous HIV care experience among those dying from HIV, we generated estimates of HIV-related deaths across stages of HIV care using mathematical models calibrated to HIV epidemic and HIV diagnosis, care, and treatment data from settings with mature ART programmes.

Mathematical models

We used mathematical models representing the HIV epidemic and HIV care and treatment in four countries: Rwanda, Kenya, Malawi, and South Africa. The model for each country was independently developed and calibrated to national level estimates of HIV prevalence and ART coverage and country-specific data about HIV diagnosis, linkage to and retention in care, ART initiation, and disengagement from ART programmes. Table 4.1 describes the settings represented by each of the models and changes in CD4 ART eligibility thresholds.

The models were independently developed and each makes subtly different assumptions about patient behaviours related to HIV care seeking in order to reconcile available data about HIV testing, ART coverage, linkage, and retention in care. Table 4.2 summarises key assumptions for each model. Different model assumptions to some extent reflect the true differences across the four settings, but also highlight that available HIV care cascade indicators can be explained through different underlying assumptions about the factors that determine HIV care seeking, which may affect projections for future epidemic and mortality trends.

Table 4.1: Summary of mathematical models and HIV epidemic in 2015

Model	Country	ART CD4 eligibility [†]	HIV prevalence ^{††}	% HIV+ diagnosed ^{††}	% HIV+ on ART ^{††}
Bendavid	Rwanda	'03-'12: <350 '13-: <500	3%	81%	57%
Olney	Kenya	'04-'10: <200 '11-'14: <350 '15-: <500	4%	83%	49%
HIV Synthesis	Malawi	'04-'11: <250 '11-'14: <350 '14-: <500	10%	78%	58%
EMOD	South Africa	'03-'10: <200 '11-'14: <350 '15-: <500	17%	76%	50%

[†] All models additionally allow for ART eligibility based on the presence of WHO Stage 3/4 conditions or opportunistic infections. HIV Synthesis and EMOD additionally incorporate changes to Option B+ for pregnant women.

^{††} In the year 2015, among all adults age 15+ years.

Table 4.2: Model assumptions about stages of HIV care and the effects of HIV-related symptoms on accessing care.

	Bendavid — Rwanda	Olney — Kenya	Synthesis Transmission — Malawi	EMOD — South Africa
HIV diagnosis	<ul style="list-style-type: none"> - 10% of adults will never test. - For remaining 90%, testing rate for HIV+ adults increases over time from 0.21 per year in 2003 to 0.42 per year in 2015. 	<ul style="list-style-type: none"> - 14% of HIV+ adults are tested each year. - Person with WHO Stage 3/4 condition receive a test after a mean of 10 weeks. 	<ul style="list-style-type: none"> - Test rate dependent on gender/ pregnancy, calendar time, and presence of WHO stage 3/4 event. - In 2015, 0.2 per year for non-pregnant, asymptomatic. - Persons with WHO Stage 4 event, test at rate 2.4 per year during 3 month period in which event occurred. 	<ul style="list-style-type: none"> - Routine annual HIV testing increases over time, up to maximum of 80% of adults in 2015. - 60% probability of testing when developing HIV-related symptoms. - 60% of pregnant women receive HIV test via antenatal care.
Linkage to care	<ul style="list-style-type: none"> - Probability of linking to care increases from 70% in 2003 to 90% in 2015. - 50% of those lost from linkage will return to upon developing an opportunistic infection (OI). 	<ul style="list-style-type: none"> - 90% of newly diagnosed link to care. - Asymptomatic persons return to care rate 0.15 per year. - Previously diagnosed persons with symptoms (WHO 3/4) link/re-link to care at rate 10.1 per year. 	<ul style="list-style-type: none"> - 60% if asymptomatic; 85% if current WHO Stage 3; 95% if current WHO 4/TB. - Asymptomatic previously diagnosed persons return to care at rate 0.2 per year. - Previously diagnosed persons with WHO stage 4 re-link at rate 2.4 per year during 3 month period of event. 	<ul style="list-style-type: none"> - 85% of those testing positive link to CD4-agnostic ART staging (WHO stage, TB, pregnancy, pediatric HIV). - Among those not eligible based on WHO Stage, TB or pregnancy, 85% return for CD4 measurement. - If ART ineligible, individuals link to pre-ART with probability that increases from 46% to 63% in 2015.
Pre-ART care	<ul style="list-style-type: none"> - Individuals disengage from pre-ART care at a rate of 0.06 per year. 	<ul style="list-style-type: none"> - 90% of linked to care return for CD4 test result after 1 month. - If not ART eligible, 75% return for CD4 test after 1 year. 	<ul style="list-style-type: none"> - All linked persons have CD4 count every 6 months, with 85% probability the scheduled test is performed. - Rate of loss from pre-ART care of 0.16 per year. 	<ul style="list-style-type: none"> - Individuals retained in pre-ART monitoring test for ART eligibility every 6 months. - After each visit, individuals not ART eligible are retained in pre-ART with a 75% probability.
ART initiation	<ul style="list-style-type: none"> - Initiate immediately upon either presenting to care with OIs are initiated at the time of presentation or CD4 test below eligibility threshold. 	<ul style="list-style-type: none"> - Persons with WHO 3/4 conditions when appearing for care initiate ART immediately. - Persons eligible based on CD4 criteria results initiate ART at rate 2.5 per year. 	<ul style="list-style-type: none"> - Eligible persons (based on CD4, WHO Stage 4, pregnancy Option B+) initiate at rate 1.8 per year before 2011 and 1.2 per year after 2011. 	<ul style="list-style-type: none"> - 75% of persons determined eligible link to ART care and initiate ART after a delay of between immediate and 4 months.
Mortality on ART (in year 2015)	<ul style="list-style-type: none"> - On ART <6 mos: 21 per 1000 PYs. - On ART ≥6 mos: 11 per 1000 PYs. 	<ul style="list-style-type: none"> - On ART <6 mos: 58 per 1000 PYs. - On ART ≥6 mos: 14 per 1000 PYs. 	<ul style="list-style-type: none"> - On ART <6 mos: 16 per 1000 PYs. - On ART ≥6 mos: 11 per 1000 PYs. 	<ul style="list-style-type: none"> - On ART <6 mos: 73 per 1000 PYs. - On ART ≥6 mos: 12 per 1000 PYs.
Retention on ART	<ul style="list-style-type: none"> - Persons on ART disengage at rate 0.01 per year. - 25% of those who who are lost spontaneously return to care within 2 years. - 50% of those lost return to care upon developing an OI. 	<ul style="list-style-type: none"> - In first year on ART, disengage at rate 0.05 per year. - After first year, disengage at rate 0.02 per year. - Assume not to reinitiate ART. 	<ul style="list-style-type: none"> - Rate of interruption of ART is 0.04 per year during first 2 years. - Rate of interruption 0.02 per year after 2 years. - Rates doubled for persons experiencing drug toxicity. 	<ul style="list-style-type: none"> - ART disengagement rate is 0.033 per year. - Of those disengaging from ART, 25% are permanently lost, whereas the remaining 75% can resume ART later.

Sources of HIV-related mortality

Figure 4.1 illustrates the HIV mortality rate (number of HIV-related deaths per 1000 HIV-positive adults) over the period 2003 through 2025 if the 2015 ART eligibility and patterns of accessing HIV care continue. Overlaid are the trends in the percentage of all HIV-positive adults who are diagnosed and the percentage of HIV-positive adults who are on ART (henceforth 'ART coverage').

Between 2004 and 2015, HIV-related deaths per 1000 HIV-positive adults declined by 66% in Rwanda, 48% in Kenya, 69% in Malawi, and 44% in South Africa, as ART was scaled-up.

Figure 4.1 illustrates the share of HIV-related mortality that occurs among persons who have not initiated ART (red) compared to those who have initiated ART (blue). The fraction of HIV deaths occurring among ART experienced adults increases as care programmes scaled-up, but in 2015 still a large fraction—40% to 60% of HIV deaths—are estimated to be among persons who never initiated ART (Figure 4.2). This includes an estimated 20–30% of HIV deaths occurring among undiagnosed persons and 25%–45% of deaths among persons who were either never diagnosed or never linked to care. These patterns are consistent with the independent empirical findings in Section 3.

Figure 4.3 compares the distribution of the HIV-positive adults across a finer classification of care stages (top panel) with the distribution of HIV related deaths (bottom panel). This illustrates large differences in HIV mortality rates across care stages (Figure 4.4).

To date, persons who have disengaged from ART have contributed a modest amount to all HIV-related deaths (purple section of Figure 4.3, bottom panel), but this proportion of HIV deaths coming from this population is expected to grow substantially, contributing between 20% and 35% of all HIV deaths in the coming decade. This accords with the findings from the Western Cape, where deaths among persons disengaged from care are already becoming dominant.

Between 30% and 50% of HIV deaths are projected to occur among persons who never initiated ART, in the absence of improvements in diagnosis, linkage to care, and ART initiation.

In contrast, adults stable on ART (for >6 months) are projected to comprise the largest share of all HIV-positive adults—around 60% of all HIV-positive adults— but they contribute a much smaller proportion of HIV-related deaths (between 17% and 30%) because they have by far the lowest estimated mortality rate (between 7 and 15 per 1000 PYs).

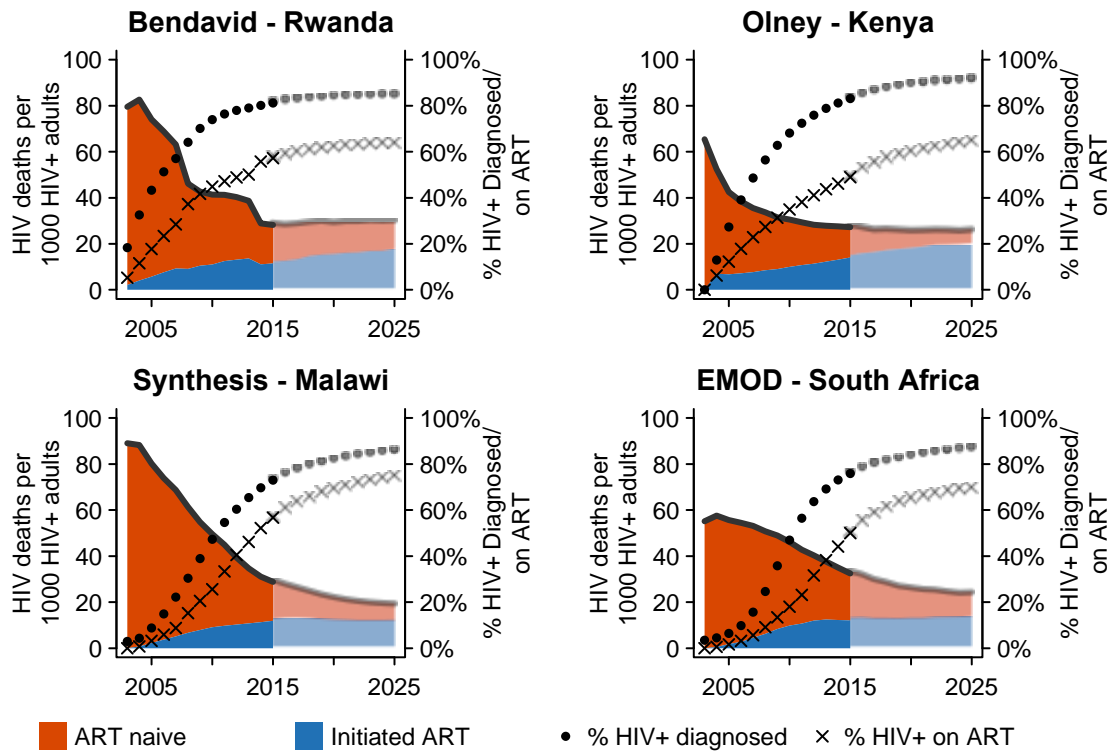


Figure 4.1: Number of HIV-related deaths per 1000 HIV-positive adults (left axis). Shading illustrates the proportion of deaths to HIV-positive adults who never initiated ART (red) and ever initiated ART (blue). Overlaid dots and crosses indicate the percentage of HIV-positive adults who are diagnosed and on ART, respectively (right axis).

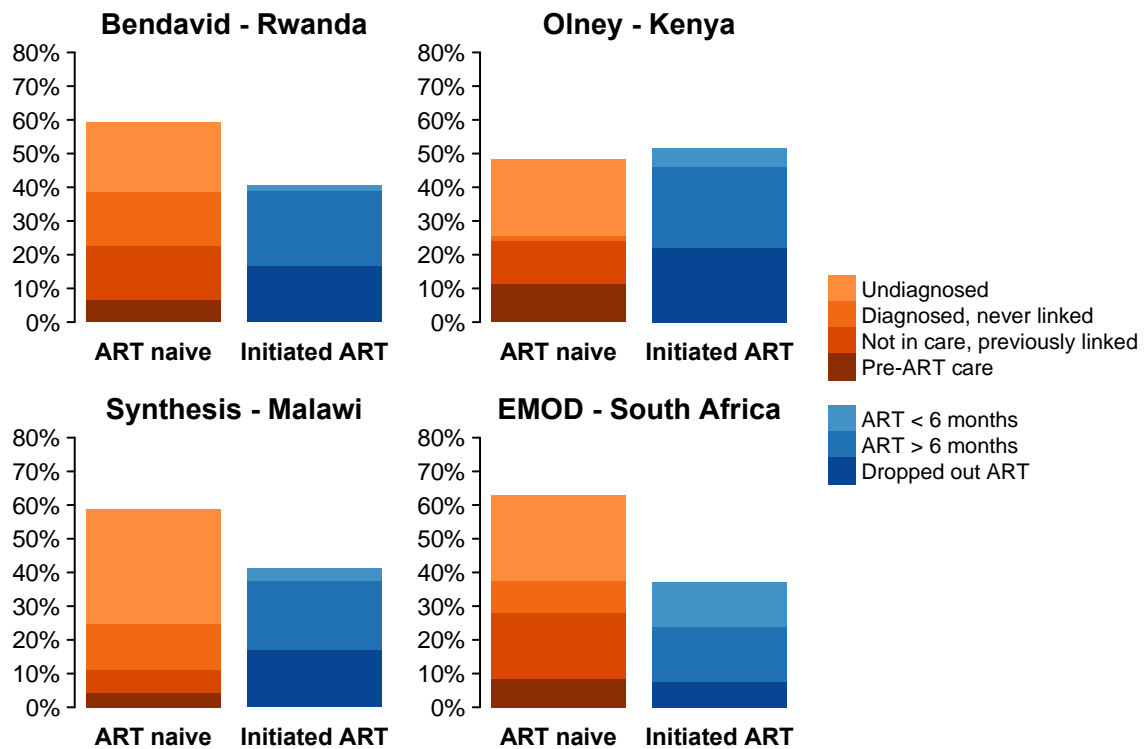


Figure 4.2: Distribution of HIV-related deaths occurring in the year 2015 across stages of HIV care.

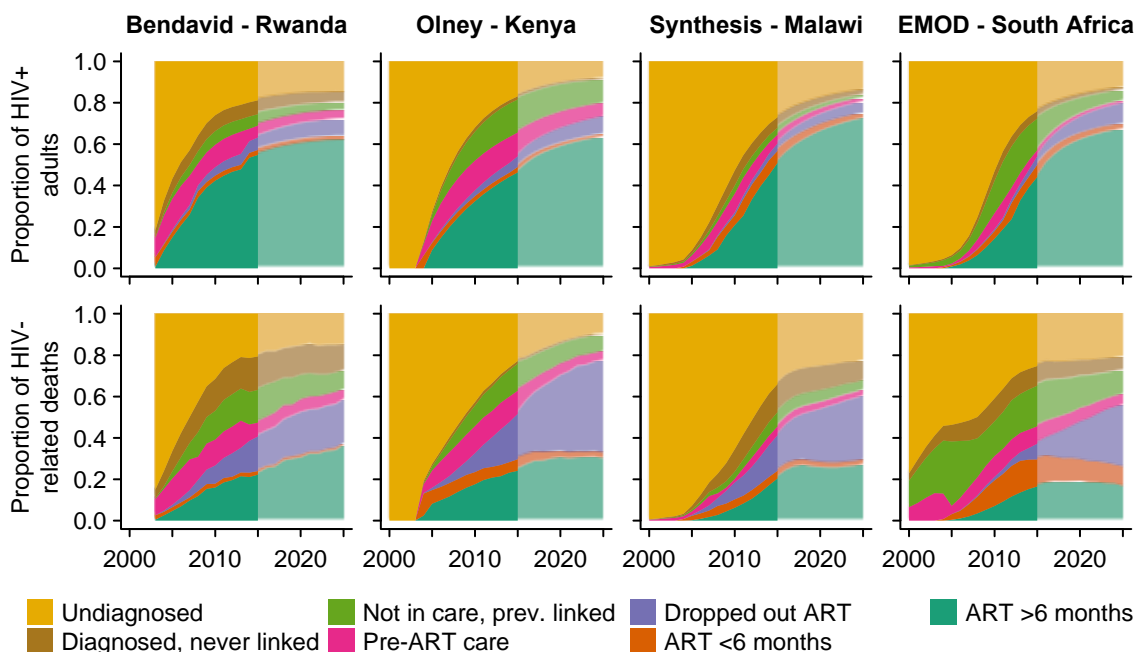


Figure 4.3: (Top) Distribution of HIV-positive adults across HIV care stages over time. (Bottom) Distribution of HIV-related deaths across HIV care stages. Translucent sections illustrate projections for HIV mortality over the decade from 2016 through 2025, assuming a continuation of current ART eligibility (CD4 <500) and patterns of accessing care.

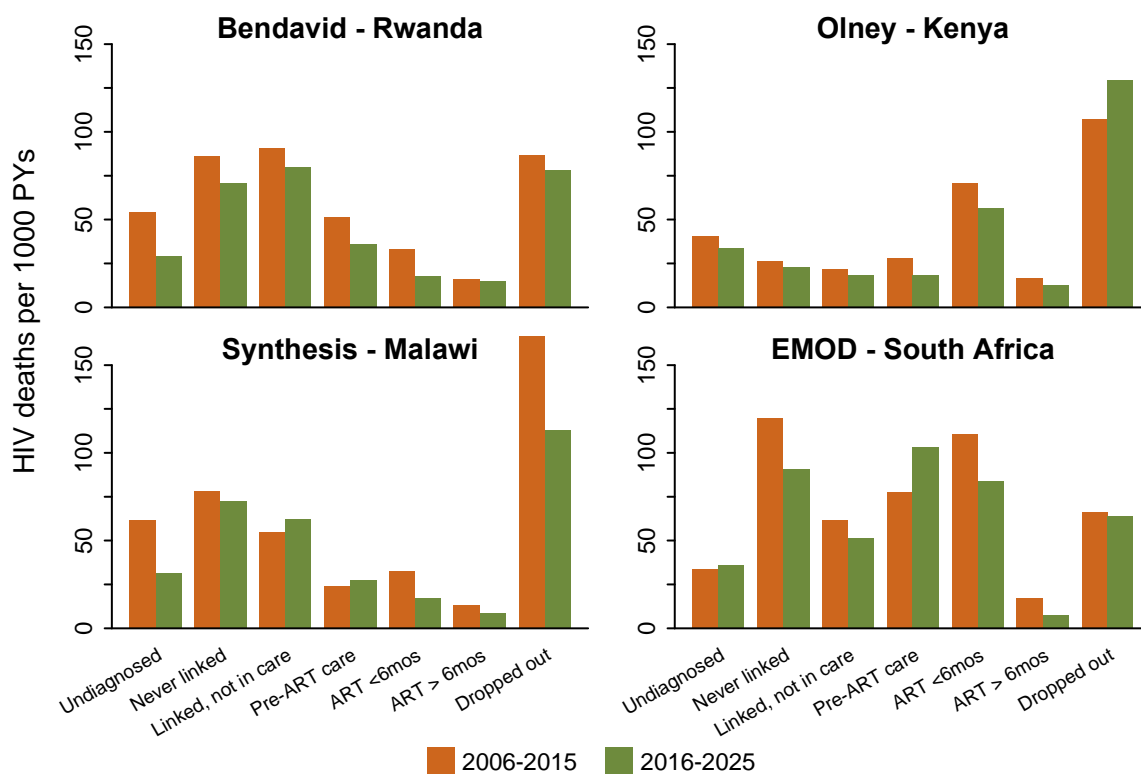


Figure 4.4: Excess HIV-related mortality rate in each stage of care over the periods 2006–2015 and 2016–2025.

5. ‘When to Start ART’ – The Pragmatic benefits of immediate ART initiation

Data from Western Cape and estimates from mathematical models illustrate a substantial contribution to HIV-related deaths occurring among persons who were at one point linked to care and subsequently lost or return very late. Models estimated that between 10% and 30% of HIV deaths in 2015 occurred among persons who had at one point been linked to care but never initiated ART. Over the next decade this group will account for between 9% and 22% of HIV-related deaths if current guidelines continue in the absence of strategies that relink HIV+ persons to ART (Table 5.1).

Table 5.1: Projected percentage of HIV-related deaths among persons ever linked to care but did not initiate ART over 2016–2025.

Rwanda	Kenya	Malawi	South Africa
18%	15%	9%	22%

While direct therapeutic benefits of earlier ART initiation (above CD4 >500) could be modest and the population-wide HIV prevention benefits are still being evaluated in trials, an unquantified potential benefit of immediate ART initiation irrespective of CD4 count are those derived from preventing the losses that occur among patients in pre-ART care.

Strictly, the extent to which immediate ART would ameliorate the mortality resulting from losses incurred during pre-ART care depends on the retention of these same patients on ART compared to pre-ART. Although data is lacking on this precise point, results from the RapIT trial in Johannesburg were very positive about the effectiveness of same-day ART initiation as a strategy for improving retention in care: among ART eligible patients, 98% initiated ART within 90 days of those randomised to receive point-of-care CD4 eligibility assessment and same-day ART initiation if eligible, compared to only 72% randomised to standard clinic initiation procedures (Rosen *et al.* CROI 2015); and clinic attendance after ART initiation and viral suppression after 6 months were the same among both arms.

The effect of immediate ART initiation on HIV mortality

We used models for Kenya, Malawi, and South Africa to investigate how a strategy in which all patients presenting for HIV care are immediately initiated onto ART would affect HIV-related mortality over the ten-year period 2016 through 2025.

Model simulations assume that HIV-positive patients linking to care initiate ART immediately instead of being referred for CD4 testing, and assume that such patients are retained on ART similarly to patients eligible under current guidelines (although data on this point is currently lacking). These simulations do not assume any other changes to HIV testing, linkage to care resulting from immediate ART eligibility.

Figure 5.1 illustrates the estimated percentage reduction in HIV-related deaths over the decade 2016–2025 resulting from immediate ART initiation. Immediate ART averted 9% of HIV related deaths in Kenya, 6% in Malawi, and 14% in South Africa. (Note that these values are less than the values given in Table 5.1 as some of the deaths that would have occurred among those disengaging following linkage in Table 5.1 would not be averted by immediate ART initiation.)

Over the period 2015-2025, the vast majority of that benefit comes from initiation of more people on ART and them starting earlier (Figure 5.2). Over the longer-term, the additional benefit of reduced transmission may become an important factor as well.

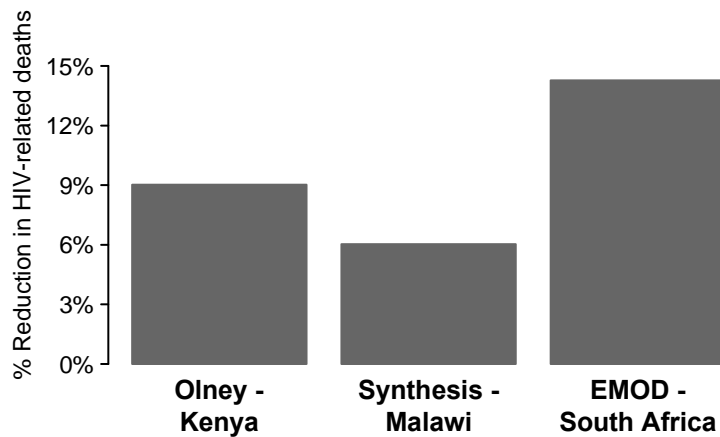


Figure 5.1: The percentage reduction in HIV-related deaths over the period 2016 through 2025 associated with immediate ART initiation irrespective of CD4 cell count compared to continuing CD4 <500 eligibility criteria. Other than immediate ART initiation for patients linking to care, simulations do not assume any other changes to HIV testing, linkage to care resulting from immediate ART eligibility. Each of the models also incorporate effects of reduced HIV transmission. Olney and Synthesis assume modest reductions in the risk of HIV-related morbidity or mortality for persons initiating ART with CD4 >500 (which is already very low in the absence of ART), while EMOD assumes no immediate therapeutic benefit of immediate ART initiation.

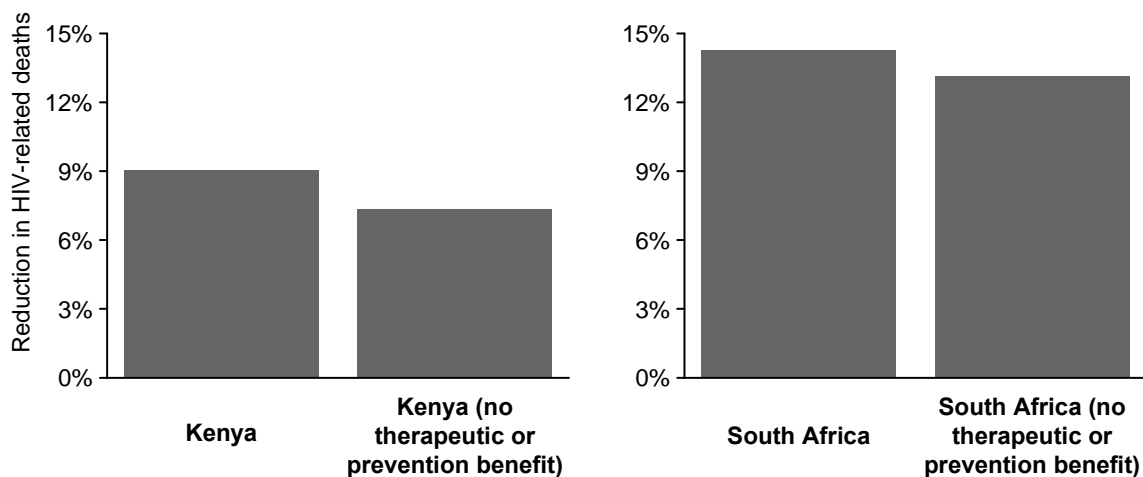


Figure 5.2: The effect of immediate ART initiation on HIV-related mortality during 2016–2025 assuming no therapeutic benefit from earlier ART initiation (i.e. untreated persons with CD4 >500 experience the same mortality as those on ART) and no prevention benefit (i.e. the same number of new infections occur each year irrespective of treatment policy).

6. Defining priorities for improving HIV care

HIV programmes should commit resources to where they are expected to generate greatest health gains in the population (i.e. so that resources are used 'cost-effectively'). This will require combining information about where HIV deaths are occurring, described in sections 3 and 4 of this report, with accumulating evidence about which interventions can effectively reduce HIV deaths and the costs of these interventions.

With good data on programs and the estimates of the cost and impact of a range of interventions, it is possible to provide further evaluation of different options for strengthening the care cascade.

We calibrated a mathematical model to a longitudinal dataset from the Academic Model Providing Access To Healthcare (AMPATH) program in Western Kenya. These data describe the routes into care, losses, and clinical outcomes. We simulated the cost and impact of interventions acting at different stages of HIV care, including improvements to diagnosis, linkage to care, retention and adherence on ART, and immediate ART eligibility and universal test-and-treat. We quantified impact in health in terms of DALYs averted over a period 2010-2030, incorporating reduced death and morbidity from HIV infection, and any reductions in numbers newly infected.

We found that no individual intervention on the cascade is expected to avert more than 10% of DALYs (Figure 1). This small impact is because any single intervention is confounded by other weaknesses in the cascade. The changes to better retain patients on ART and to remove the pre-ART stage of the cascade by initiating ART for any HIV-positive person as soon as they are diagnosed, give greater impact than any other single intervention.

However, a combination of interventions (including improved testing and linkage, together with pre-ART and ART outreach strategies) was estimated to generate a much larger impact and it is likely (based on provisional estimates of cost) to avert DALYs cost-effectively. The combination of HIV care interventions was estimated to generate a similar level of health gains as a radical expansion to 'Universal test and treat' over this time frame but at substantially lower cost. Switching to a policy of immediate ART initiation in addition to this combination of 'cascade interventions' would lead to even larger health gains.

These results show that moving to a UTT strategy with a leaky cascade would not maximize health benefits in a resource-limited setting, whereas a combination of interventions that strengthen the cascade including a move to immediate ART initiation could generate substantial health gains cost-effectively.

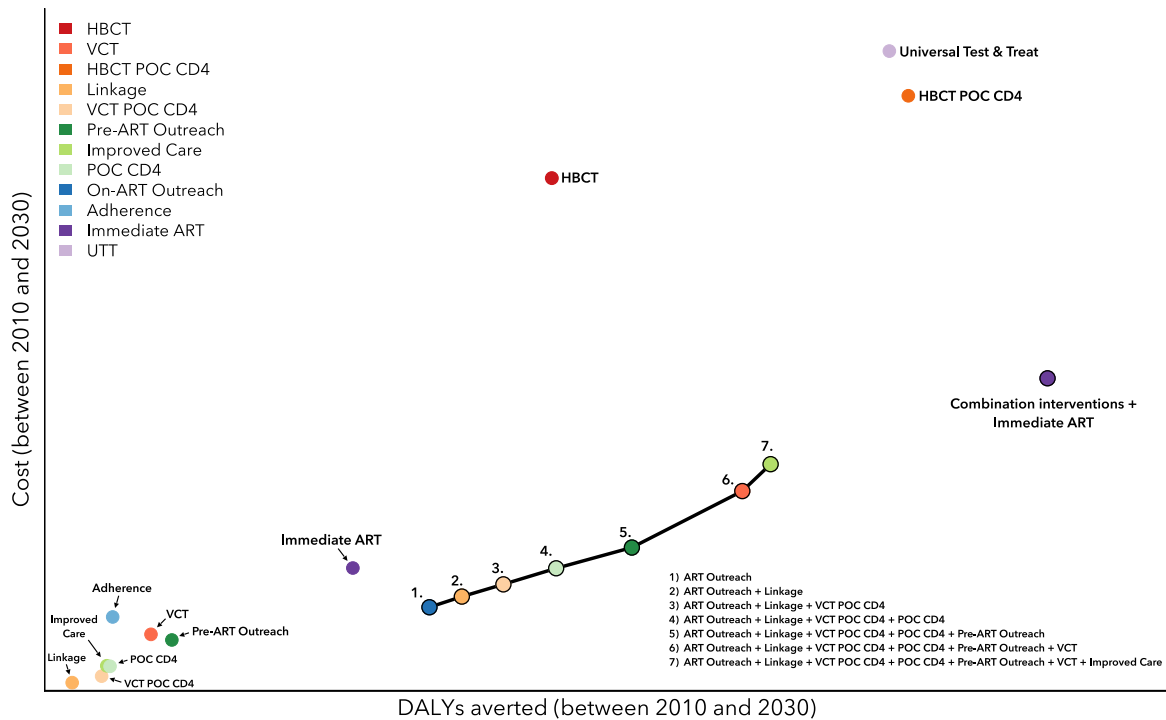


Figure 6.1. DALYs averted and additional cost of care for individual interventions between 2010 and 2030. Cost is estimated by calculating the additional cost of care relative to baseline between 2010 and 2030, and impact through calculating the number of disability-adjusted life-years (DALYs) averted relative to baseline in the same period. Points linked together indicate combinations of interventions (listed within the figure), otherwise interventions applied individually. The interventions are: Home-based counselling and testing (**HBCT**) of 90% of the population every 4 years, with patients more likely to link to care if previously diagnosed; Enhanced voluntary counselling and testing (**VCT**) that increases the rate of testing through VCT by 25%; Home-based counselling and testing with point-of-care CD4 testing (**HBCT POC CD4**) is the same as HBCT but with the addition of POC CD4 testing which increases rate of linkage to care; The **linkage** intervention reduces the risk of not linking to care by 50%; **VCT POC CD4** provides POC CD4 testing for all persons testing through VCT, increasing the chance they link to care; **Pre-ART Outreach** returns 20% of patients that have been lost from pre-ART care every year; **Improved Care** reduces the risk of being lost from pre-ART care by 50%; **POC CD4** provides point-of-care CD4 testing to all persons in pre-ART care; **On-ART Outreach** returns 40% of patients lost from ART care every year; **Adherence** reduces the risk of not adhering to ART and failing to achieve viral suppression by 50%; **Immediate ART** removes pre-ART care, providing immediate treatment for all individuals entering care; Universal test and treat (**UTT**) combines immediate ART with HBCT.

7. Conclusions

Understanding the sources of HIV mortality in settings where ART is widely available is essential for assessing what interventions could be implemented to further reduce HIV mortality and morbidity and maximise the investments in HIV care and treatment. As ART coverage reaches high levels in many settings in sub-Saharan Africa, the majority of HIV-positive adults are on ART. However, adults on ART for six months or more are responsible for a relatively smaller proportion of HIV-related deaths because mortality rates are much higher among persons who are not actively engaged in care. The implication of this is that interventions focused on diagnosing, linking and retaining patients in care and on ART may generate greater health benefits than interventions focused on improving care for patients stably on ART.

Using models, we estimated that immediate ART initiation irrespective of CD4 cell count could reduce HIV deaths by 6–15% over the next decade compared to the current guidelines of initiation at CD4 <500. This results not from any assumption about better ART outcomes if patients start at CD4 cell counts >500, but from the reduced risk of patient disengagement that can occur in pre-ART care. The ‘pragmatic benefits’ should be considered when weighing the potential benefits of different ART eligibility policies and other interventions to improve HIV care.

Identifying priorities for improving HIV care requires combing information about where the weaknesses are that give rise to HIV mortality and morbidity, the main focus of this report, with additional information about what interventions can effectively ameliorate these health losses. In reality, both the weakness in care and the available interventions will be specific to local settings, and analyses such as that described in Section 6 provides an opportunity to define priorities within local contexts. The general principle is that a comprehensive approach to priority setting must consider health losses to HIV across the entire population, not just those most apparent who are engaged in care.

A substantial limitation in preparing this report was lack of comprehensive data about HIV mortality and the care experiences among those dying from HIV. We were able to assemble data from four sites in eastern and southern Africa and the vital registration system in South Africa, all in settings with relatively mature ART programmes. No data were available from lower ART coverage settings, and in these settings even data about HIV diagnosis and care were too meagre to generate model-based inferences about sources of mortality.

This report highlights that a substantial share of HIV-related mortality occurs among persons who are not in care, and this is anticipated to continue into the future. Monitoring ART programmes using clinical indicators, such as (1) viral suppression among persons on ART, (2) mortality among patients on ART, and (3) active outreach to assess mortality among ART patients lost-to-follow-up provide an incomplete picture of the population-level effectiveness of ART programmes. Population-wide surveillance of mortality and access to care should be integral to comprehensive strategies for monitoring and evaluating HIV care and treatment programmes.

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