Who Is Dying and Why?

AIDS Mortality as a Progress Metric

Sharonann Lynch
HIV & TB Policy Advisor
MSF Access Campaign

90-90-90
Targets Workshop

July 21-22, 2018 • Amsterdam

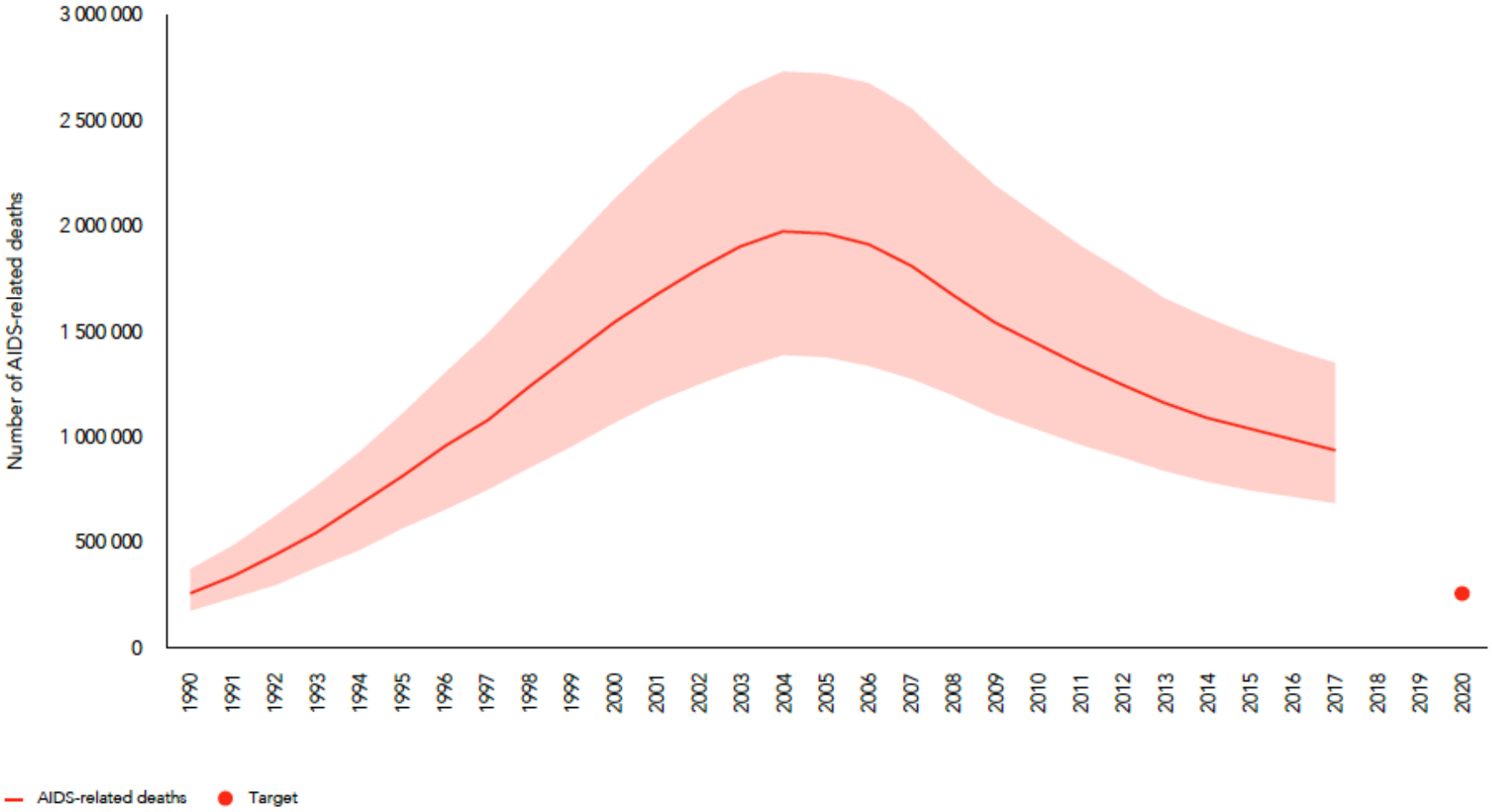
OUTLINE

1. Trends in mortality
2. Finding the RIPs among the LTFU
3. Who is dying and why
4. Preventing senseless deaths
5. Why corrected mortality rates matter

1. Trends in mortality

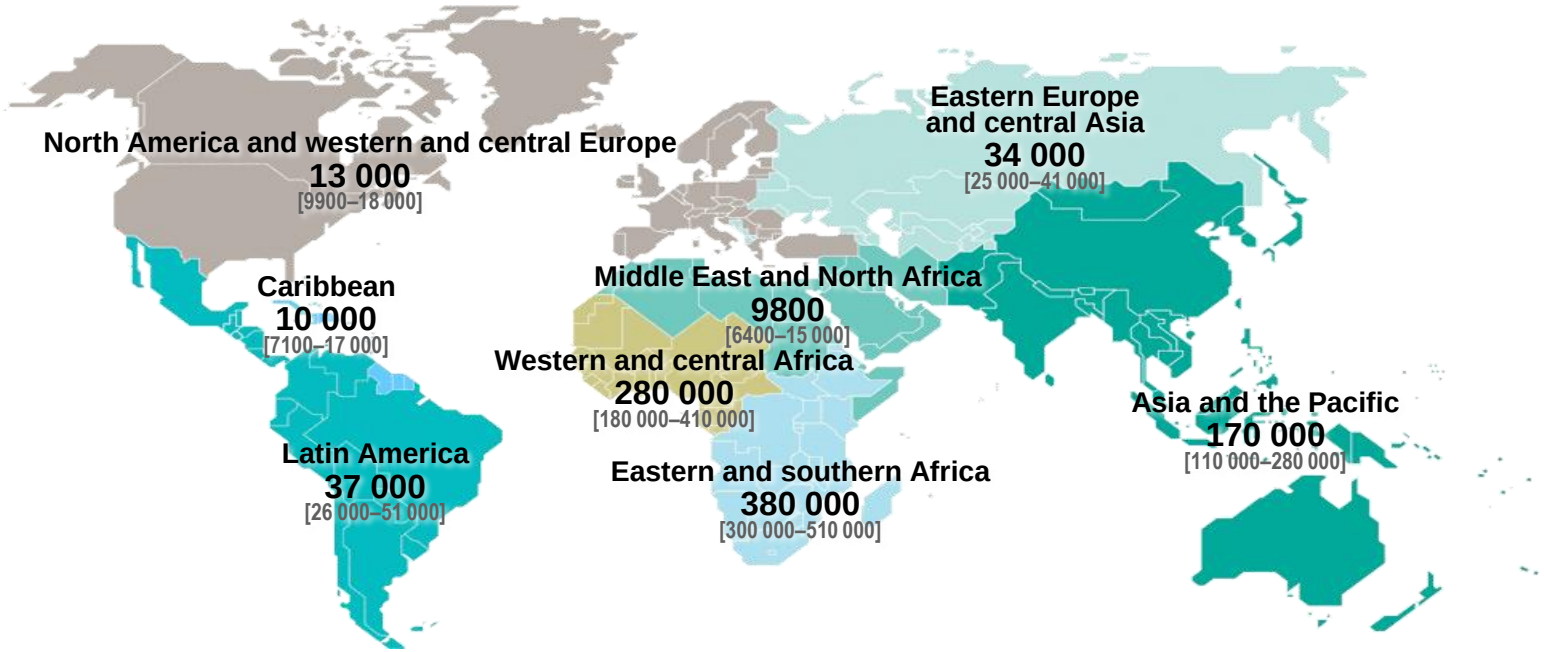
FIGURE 2.1 **Approaching a 2020 milestone**

Number of AIDS-related deaths, global, 1990–2017 and 2020 target



Source: UNAIDS 2018 estimates.

Estimated adult and child deaths from AIDS | 2017



Total: 940 000 [670 000–1.3 million]

On mortality in EECA, Middle East, North Africa:

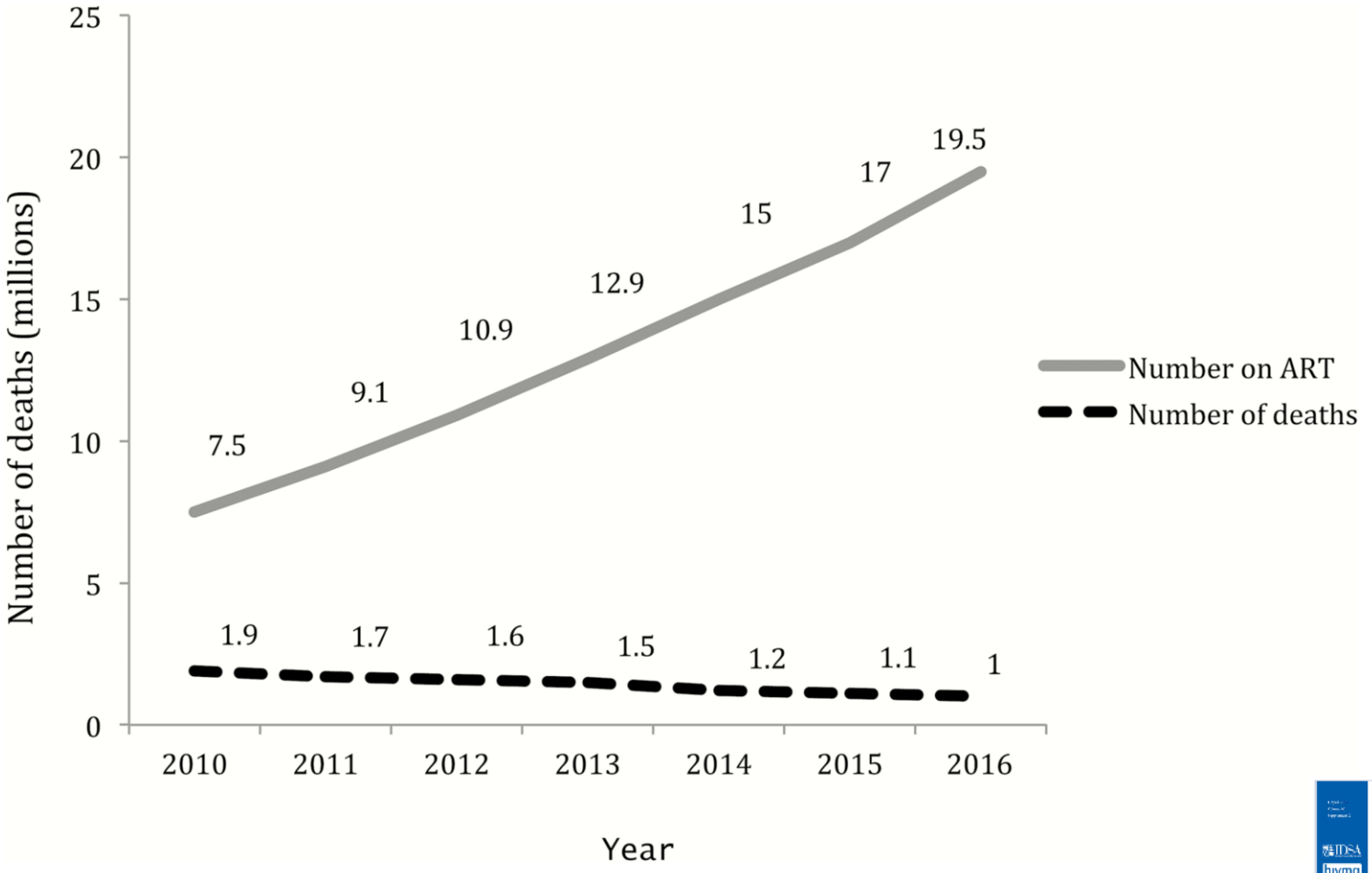
There has been no reduction in AIDS-related mortality in eastern Europe and central Asia since 2010, and deaths from AIDS-related illness increased by 11% in the Middle East and North Africa.

Mortality reductions remain higher among women than men. This gender gap is particularly notable in sub-Saharan Africa, …more men living with HIV are dying

Outside of sub-Saharan Africa, 69% deaths from AIDS-related illness were among men and boys.

SOURCE: UNAIDS

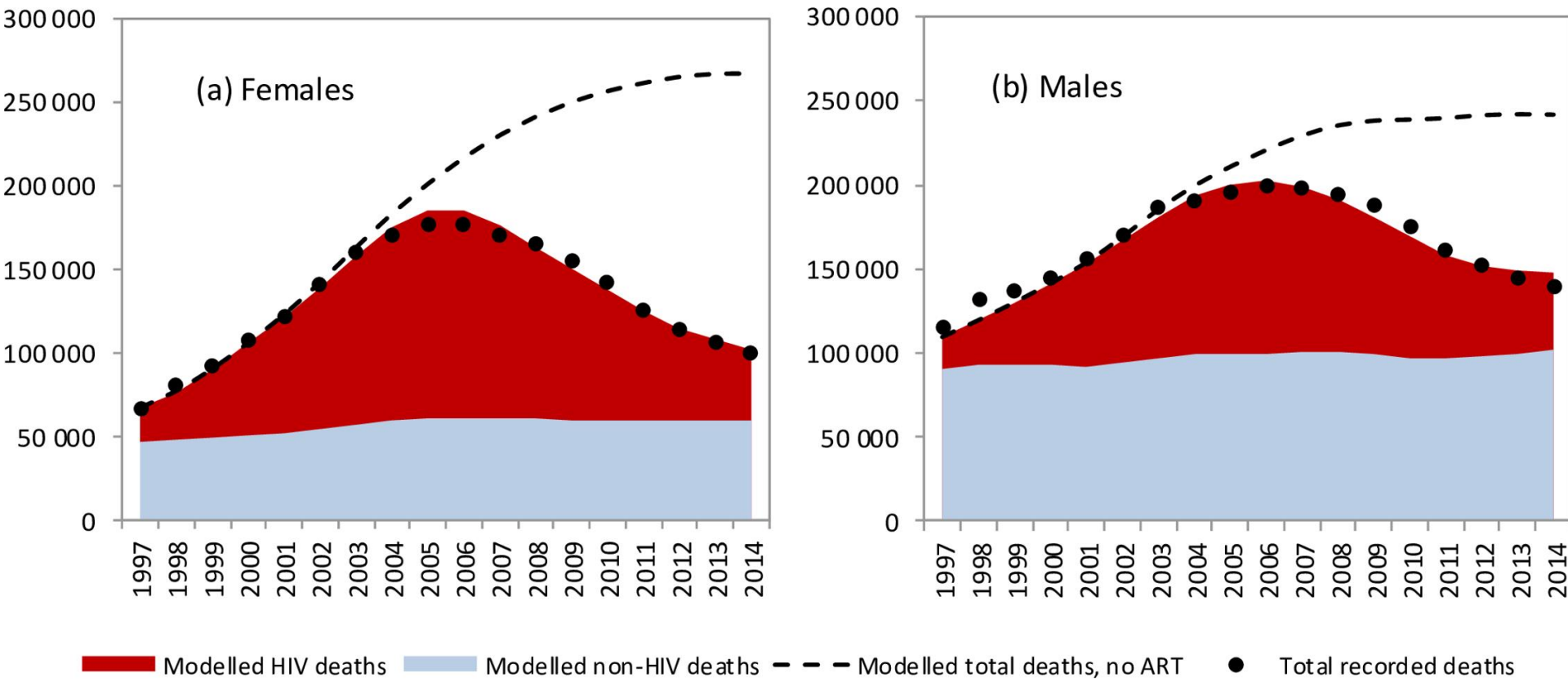
Challenge: reach as many people as possible, as quickly as possible, as early in their disease progression as possible



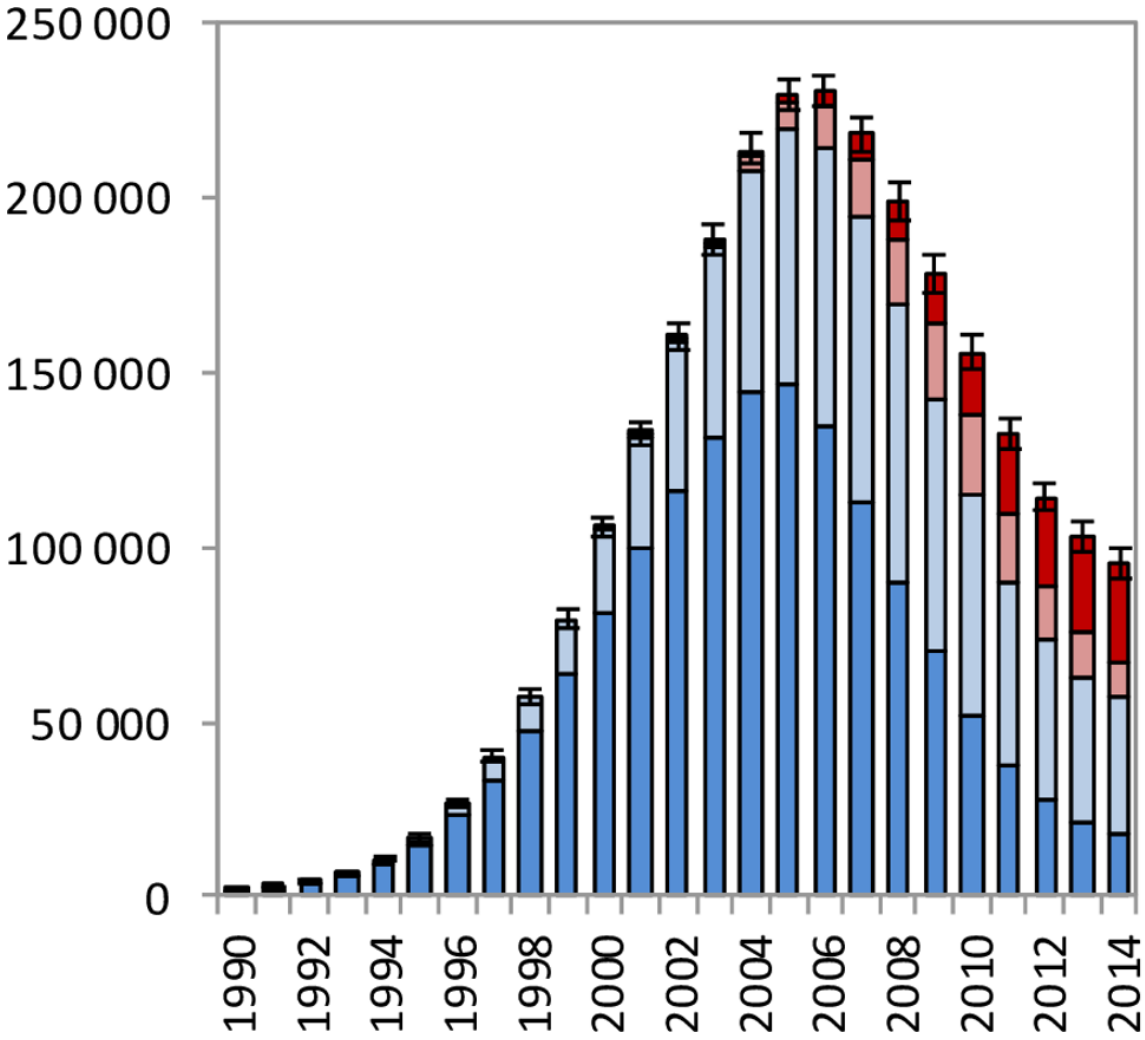
Number of patients receiving ART and number of deaths.

SOURCE: The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. Clin Infect Dis. 2018;66(suppl_2):S103-SS105. doi:10.1093/cid/cix1138

HIV deaths in South Africa, with and without ART



Johnson LF, May MT, Dorrington RE, Cornell M, Boulle A, Egger M, et al. (2017) Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med 14(12): e1002468.



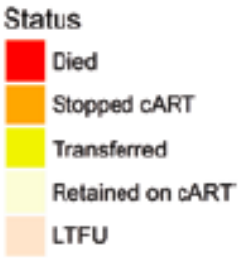
Est adult HIV deaths in 2014:
18.3% undiagnosed individuals
41.7% diagnosed but ART-naïve
10.2% <6 months of ART
29.8% >6 months of ART

HIV-related deaths in adults for the years 1990–2014 by level of engagement in HIV care
Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study.

Johnson LF, May MT, Dorrington RE, Cornell M, Boulle A, Egger M, et al. (2017) Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med 14(12): e1002468.

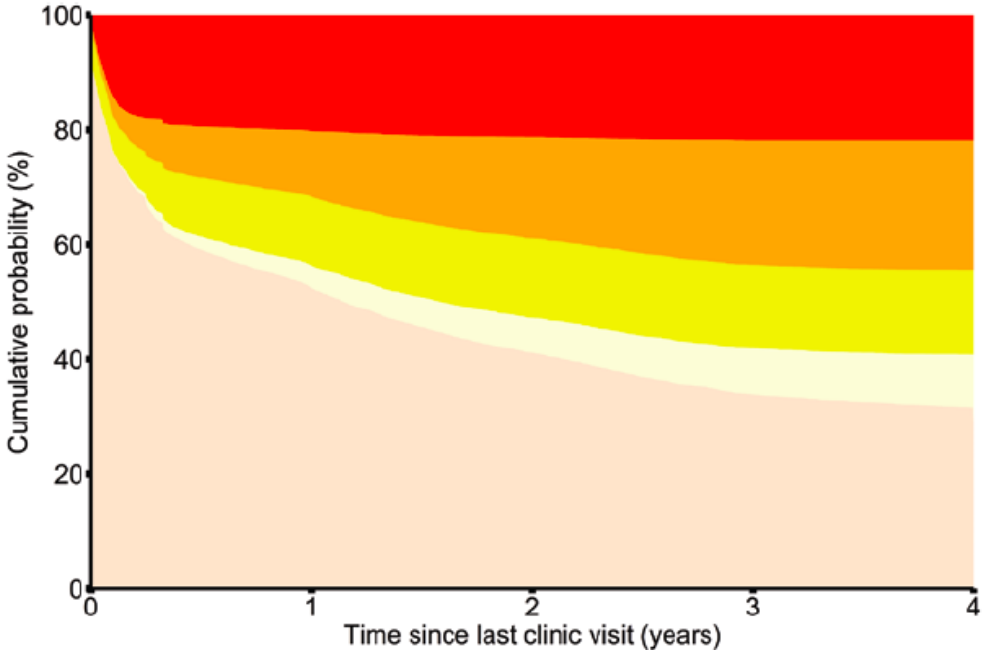
2. Finding the RIPs among the LTFU

Tracing loss to follow up



4 years after the last clinic visit

- **21.8% known RIP**
  (95% CI, 20.8%–22.7%)
- **31.6% could not been found**
  (95% CI, 30.6%–32.7%)
- **22.6% alive but stopped ART**
  (95% CI, 21.6%–23.6%)
- 14.8% transferred out
  (95% CI, 14.0%–15.6%)
- 9.2% remaining in care
  (95% CI, 8.5%–9.8%)



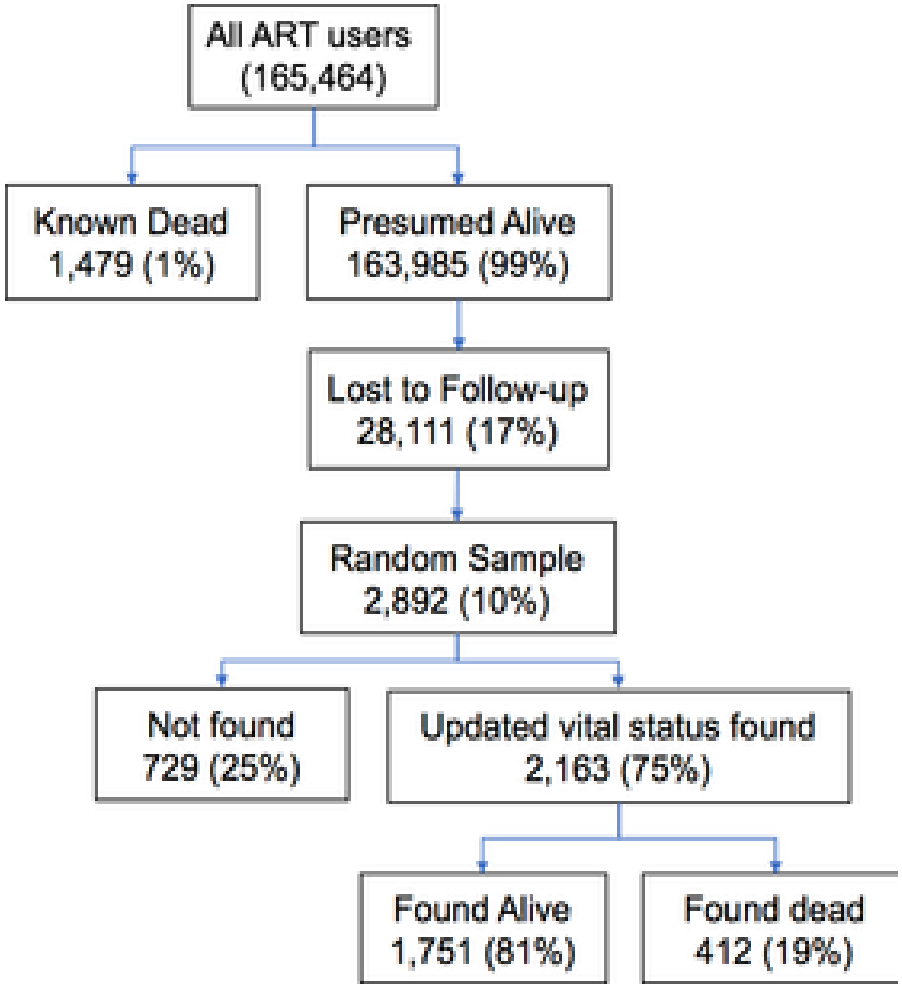
Time since last clinic visit (years)

Died	20.2 (19.3 - 21.1)	21.3 (20.3 - 22.2)	21.8 (20.8 - 22.7)	21.8 (20.8 - 22.7)
Stopped cART	11.6 (10.8 - 12.3)	17.7 (16.8 - 18.6)	21.7 (20.7 - 22.6)	22.6 (21.6 - 23.6)
Transferred	11.9 (11.1 - 12.6)	13.8 (13.0 - 14.6)	14.6 (13.8 - 15.4)	14.8 (14.0 - 15.6)
Retained on cART	4.0 (3.5 - 4.4)	6.1 (5.5 - 6.6)	8.1 (7.5 - 8.8)	9.2 (8.5 - 9.8)
LTFU	52.4 (51.2 - 53.5)	41.1 (40.0 - 42.2)	33.8 (32.7 - 34.9)	31.6 (30.6 - 32.7)
Patients followed	3870	3034	2494	2333

9 studies tracing 7,377 PLWHA on ART considered LTFU across 8 sub-Saharan countries

Chammmartin F, Zurcher K, Keiser O, et al. Outcomes of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clin Infect Dis [Online]. 2018 Jun 8.

Zambia CDC



Used a representative sampling-based approach to assess mortality among PLWHA on ART

Samples representing over 165,464 ppl across 4 provinces over a 24 month period (2013-2015)

<u>Findings</u>

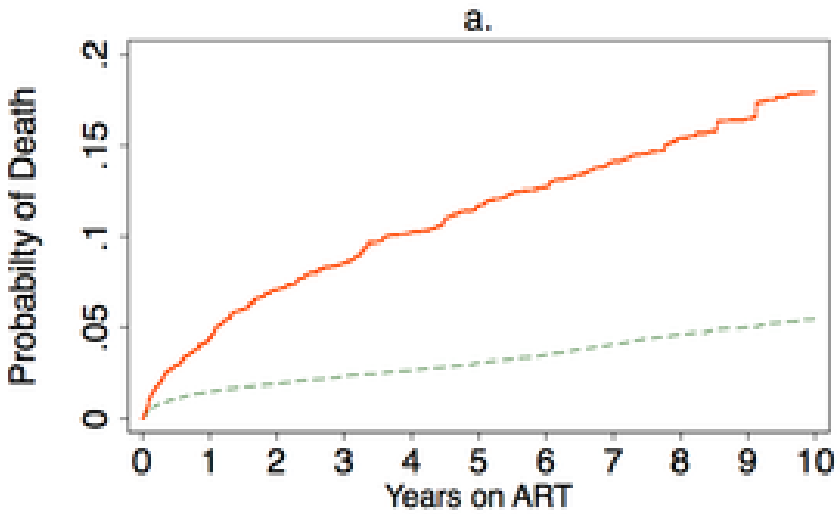
- Marked variability across geographical areas
- High site-to-site variability

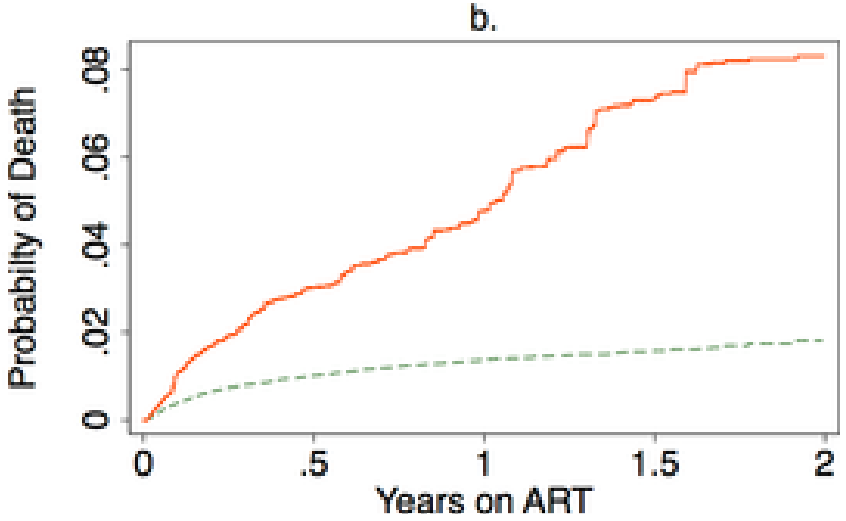
Holmes CB, Sikazwe I, Sikombe K, et al. Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. PLoS Med. 2018;15(1):e1002489.

Naïve and revised mortality estimates

(A) cumulative incidence of mortality among all ART users (*N* = 165,464)

(B) Cumulative incidence of mortality among new ART users (*N* = 49,129)





Findings

- 38.1% of deaths among PLWHA in first year on ART
- 61.8% among people on ART longer > 1 year

Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, et al. (2018) Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. PLOS Medicine 15(1): e1002489. https://doi.org/10.1371/journal.pmed.1002489

Intensive follow-up in Zambia corrects mortality figures

- **Facilities reporting high 2-year LTFU rates (40–50%)**
- **“meaning that up to half of patients at particular sites had unknown outcomes.”**
- **“passive reporting of deaths” - average of 15–20% of deaths are known to the facility**
- Found substantial underreporting of deaths. Revised numbers were 3 to 9 times higher.

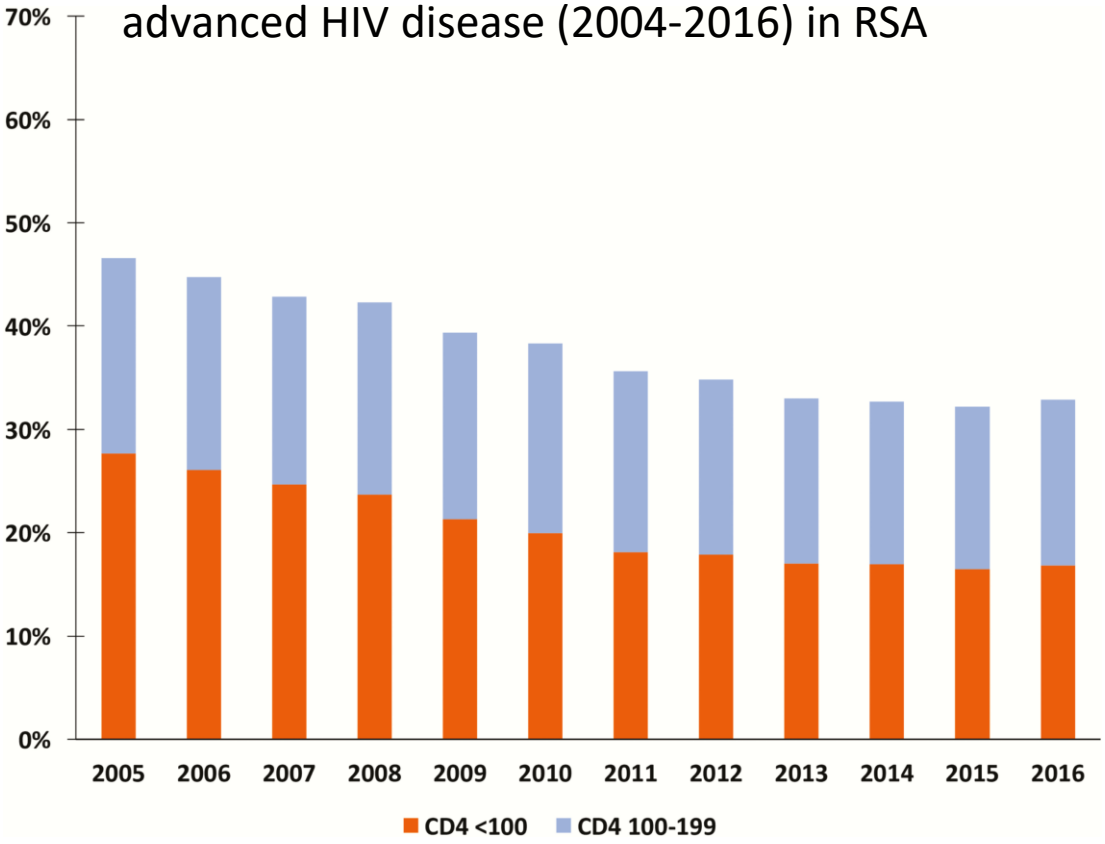
Holmes CB, Sikazwe I, Geng E. We need to monitor mortality to improve public health programs: here’s why and how to do it. International Health [Online]. 2018 Jul 17.

3. Who is dying

Proportion of PLWHA presenting with CD4 counts <200, <100, and <50 cells/µL has stayed roughly the same since 2010 (IeDEA and COHERE: among 951,855 PLWHA, across 55 countries)

IeDEA and COHERE Cohort Collaborations. Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs. *Clin Infect Dis* 2018; Jan 25.

Proportion **entering care** with advanced and very advanced HIV disease (2004-2016) in RSA



Among 654,868 PLWHA entering care in 2016 in South Africa:

- Almost a third (32.9%) had advanced HIV disease

- 16.8% had very advanced HIV disease

- Men almost twice as likely as women (23.1% vs 12.6%) to enter care with very advanced HIV disease.

Carmona S et al. Persistent High Burden of Advanced HIV Disease Among Patients Seeking Care in South Africa's National HIV Program: Data From a Nationwide Laboratory Cohort. Clin Infect Dis. 2018;66(suppl_2)

(South Africa) Increased proportion of PLWHA presenting in 2016 with CD4<50 are **ART experienced**: from 14.3% in 2008 to 56.7% in 2017

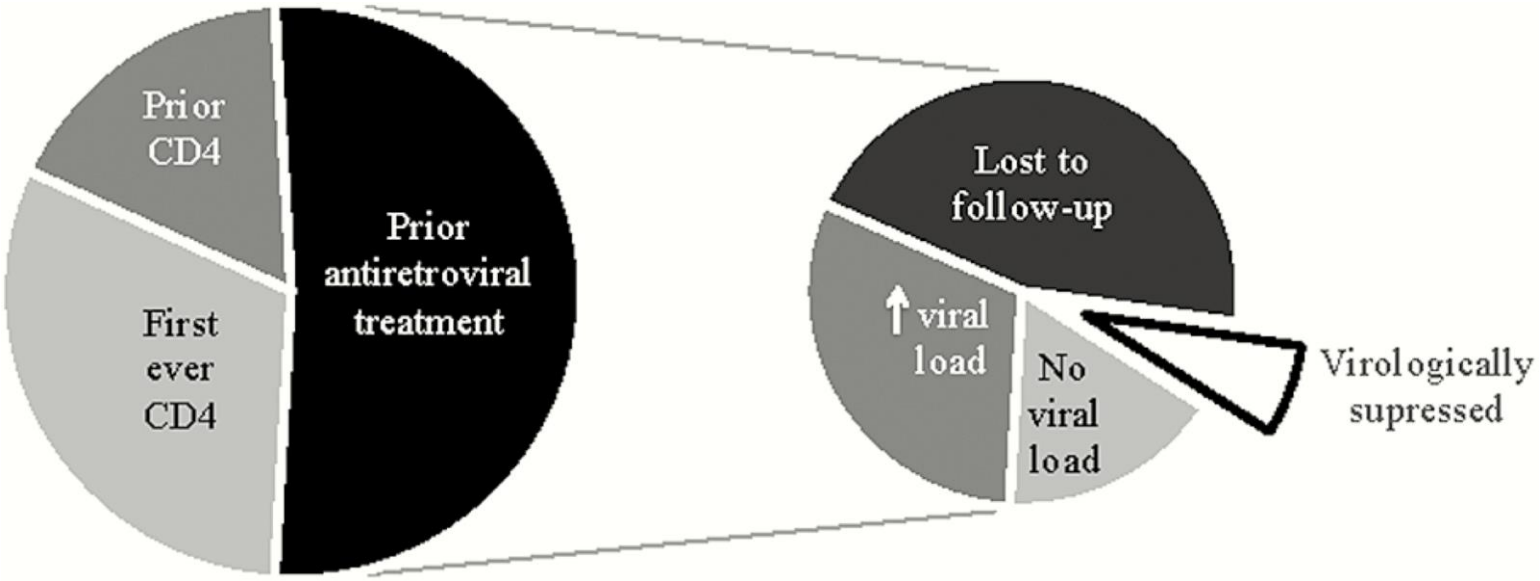
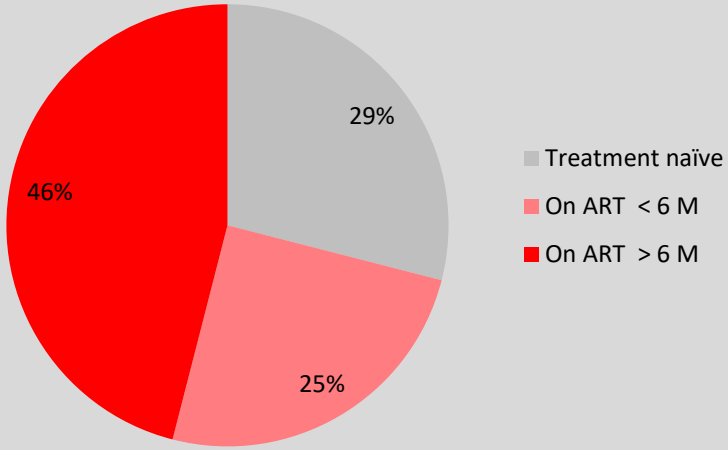


Figure: Distribution of prior CD4 count testing, antiretroviral therapy (ART), ART retention, and recent virologic status in PLWHA presenting in 2016 with a CD4 count <50 cells/µL, Western Cape province, South Africa

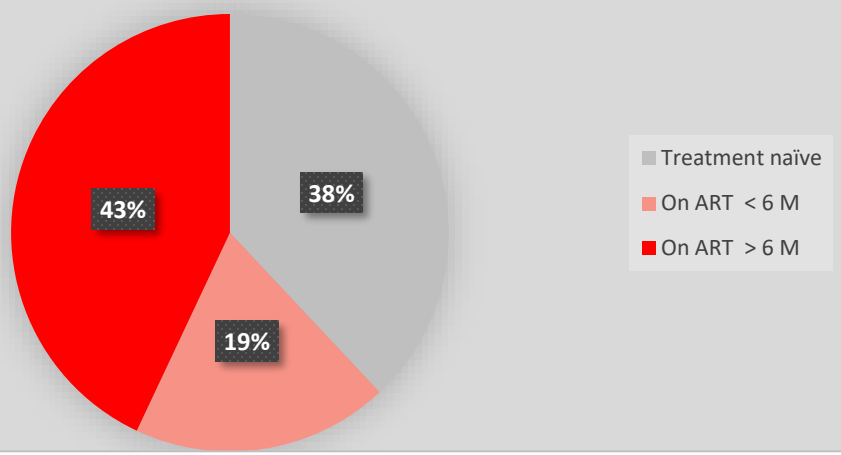
Osler M, Hilderbrand K, Goemaere E et al. The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. Clin Infect Dis. 2018;66(suppl_2):S118-S125. doi:10.1093/cid/cix1140

Admission profile by ART status in 4 referral units hospitals supported by MSF

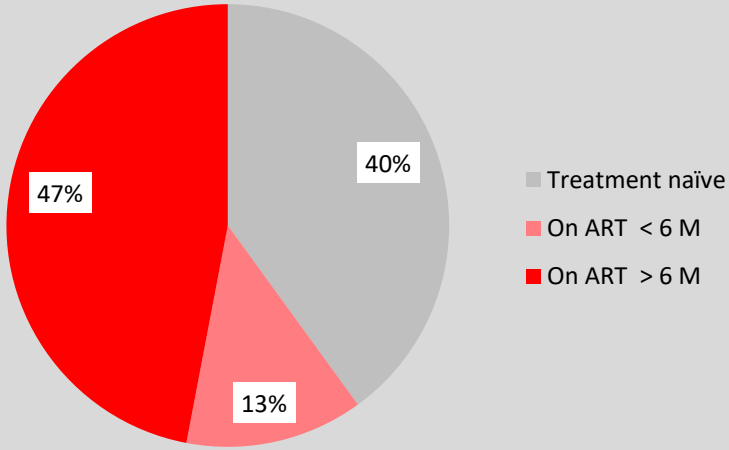
CHK, DRC (n=2210), 2015 - April 2017



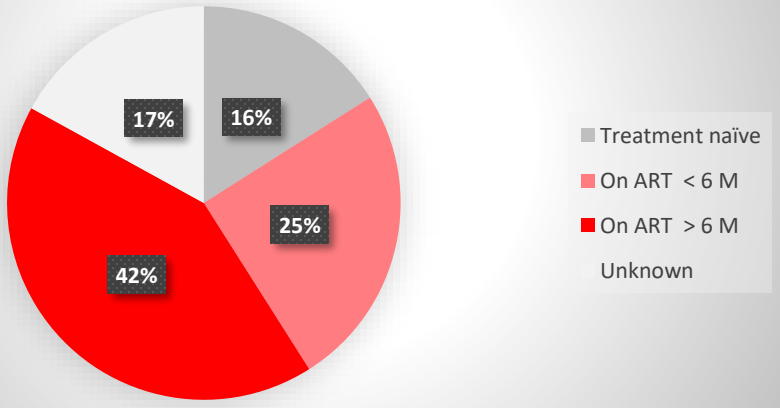
Donka Hospital, Guinea (n=588) Jan -dec 2017



Homa Bay Hospital, Kenya (n=244), Dec 2014 - March 2015



Nsanje Hospital, Malawi (n=734, May 2016 - Dec 2017



Among newly starting treatment deaths:
50.3% no history of missed visits
14.0% while late
31.7% while lost

Among longer on ART deaths:
8.8% always in care, at RIP
13.7% late history (but in care at RIP)
29.1% in care but lost history
11.7% while late
36.7% while lost

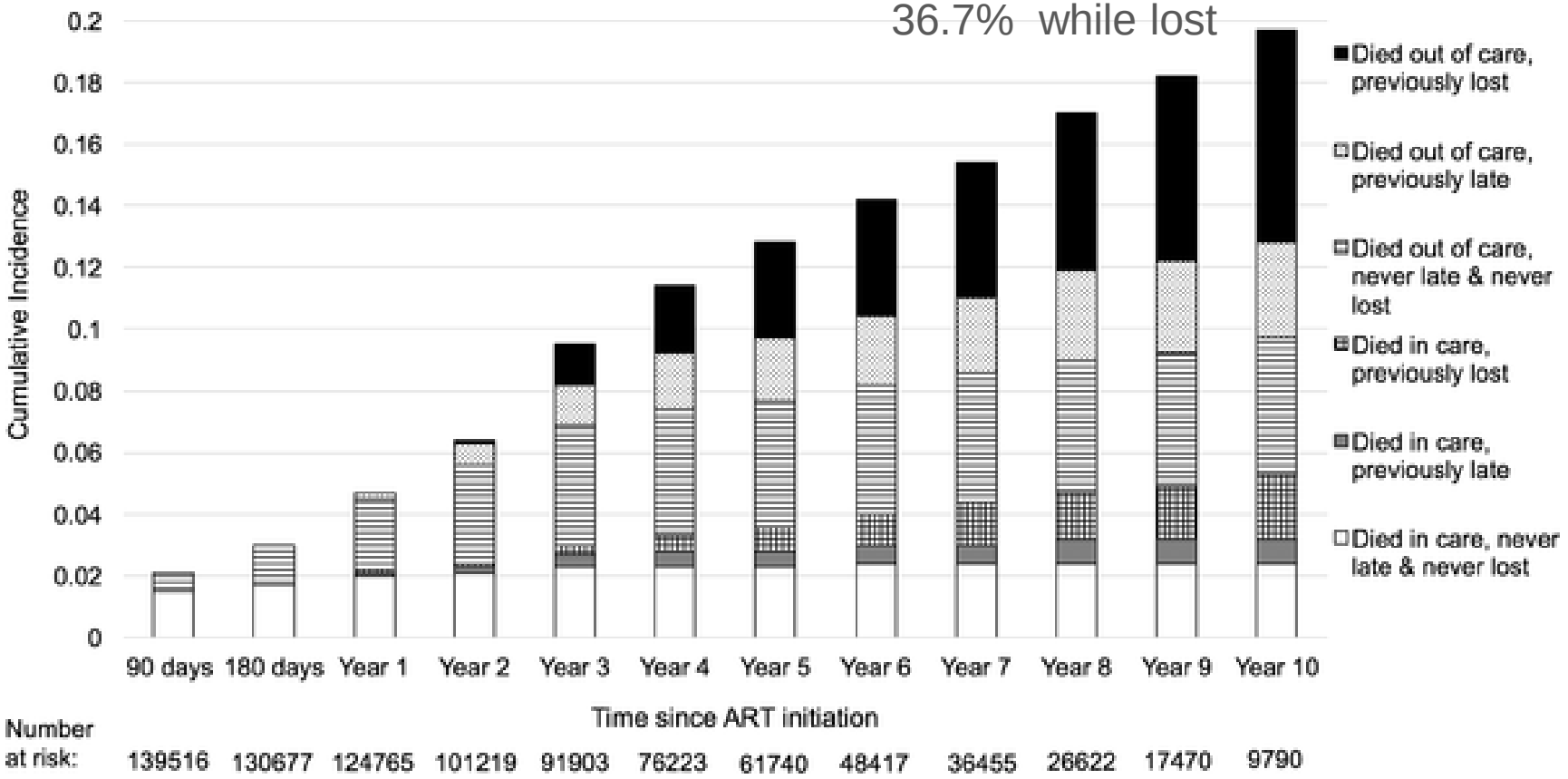


Fig 3. Proportion of patients who died after starting antiretroviral therapy (ART) by engagement status, with left truncation for individuals on ART before the study observation period (N = 165,464).

Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, et al. (2018) Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. PLOS Medicine 15(1): e1002489. https://doi.org/10.1371/journal.pmed.1002489

4. Preventing senseless deaths

Lessons

- Associated with mortality
  - Male gender
  - Low CD4 count at initiation
  - Advanced disease
  - Shorter time on ART
  - Stopping ART (even with less advanced disease and longer ART)
- What's needed
  - INTENSIVE CASE FINDING
  - Outreach and early HIV diagnosis
  - Better and rapid linkage to ART
  - Men into early ART initiation
  - Advanced HIV package of care
  - Better adherence support
  - POC tools
  - INTENSIVE ACTIVE TRACING
  - Welcome back to care…

TB FAIL

- Between 2000 and 2016, "**Among HIV-positive people, TB treatment supported by ART averted an additional 9 million deaths**." (Source WHO Global TB report)
- In 2017 3 out of 5 people starting HIV treatment are not screened, tested or treated for TB (UNAIDS Miles to Go)
- Globally, just 42% of people newly registered in HIV care were receiving tuberculosis preventive therapy.
- Among the 124 countries that reported data to UNAIDS in 2016, only 39% of the estimated number of people living with HIV who had incident tuberculosis received treatment for both HIV and tuberculosis

Non-negotiable package of OI/advanced HIV care at **PHC and inpatient facilities** to **test/treat/prevent**

→ tuberculosis
→ severe bacterial infections (SBI)
→ cryptococcal meningitis
→ toxoplasmosis
→ Pneumocystis jirovecii pneumonia (PCP)

Diagnostic	CD4
	Sputum Xpert MTB/RIF
	Urine TB-LAM
	Cryptococcal antigen screening (CrAg)
Preventive	Cotrimoxazole
	TB prophylaxis - CTX, isoniazid, & pyridoxine in FDC -3HP (3 months of weekly INH + rifapentine)
	Antifungal preemptive therapy for CrAg positive)

5. Why corrected mortality matters

Chaudhury S et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25070
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25070/full | https://doi.org/10.1002/jia2.25070

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Equity of child and adolescent treatment, continuity of care and mortality, according to age and gender among enrollees in a large HIV programme in Tanzania

Sumona Chaudhury[1,2§], Ellen Hertzmark[2], Aisa Muya[3], David Sando[2,3], Nzovu Ulenga[3], Lameck Machumi[3], Donna Spiegelman[1,2] and Wafaie W Fawzi[1,2]

[§]**Corresponding author:** Sumona Chaudhury, Department of Global Health and Population, Harvard TH Chan School of Public Health, 1635 Tremont Street, Boston, Massachusetts 02120, USA. Tel: +1 617 642 4451. (sumona@mail.harvard.edu)

"Young paediatric patients were at greater risk of early death, being almost twice as likely to die within 90 days.
Males were at greater risk of early death once initiated on ART (HR 1.35, 95% CI 1.09, 1.66))
Females in late adolescence were at greatest risk of death > 90 days after entering pre-ART/ART (HR 2.44 [1.60, 3.74] <0.01).
Late adolescents demonstrated greater non-engagement in care (RR 1.21 (95% CI 1.16, 1.26)).
Among both males and females, early paediatric and late adolescent groups experienced significantly greater loss to follow-up."

Why corrected mortality matters

- Systemic changes needed in measuring mortality
  - Civil registration and vital statistics systems
- Not “LTFU prevention,” but rather “death prevention”
- Highlights gaps in equity, services, to inform better policy and corrective action
  - “mortality across facilities ranged from 0 per 100 person years to 13.4 per 100 person years, even though the facilities in theory receive similar support”
  - Needs of populations - Young paediatric and late adolescent age groups at increased risk of late diagnosis, early death, delayed treatment initiation and loss of continuity of care
- More accurate reflection of the state of ART within the health system at national, provincial, an d facility levels

- **Mbeki's denialism and inaction resulted in more than 330,000 deaths in South Africa from 1999 to 2007**
- In the 2000–2014 period, if South Africa had moved swiftly to implement WHO guidelines
  - 2.20 million (95% CI: 2.00 million–2.37 million) fewer HIV-related deaths
  - 6.15 million life years that were actually saved and the 8.80 million life years that could have been saved

Chigwedere P, Essex M. AIDS denialism and public health practice. AIDS Behav. 2010;14(2):237–47
Johnson LF, May MT, Dorrington RE, Cornell M, Boulle A, Egger M, et al. (2017) Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med 14(12): e1002468. https://doi.org/10.1371/journal.pmed.1002468

- Model-based comparison of different ”scale-back strategies” based on hypothetical reduction of international funding for HIV in South Africa and Côte d’Ivoire
  - No New ART
  - Late Presentation
  - ART 0.350*10^9 cells/L
  - reduced retention
  - no viral load monitoring
  - no 2nd line ART
- For example, although a strategy of decreased case identification (Late Presentation) reduces the HIV program budget (RSA 13%, CI 13%), deaths are projected to increase (RSA 22%, CI 15%).
- **“reverse enormous strides made over the last 20 years in curbing the global HIV epidemic and in improving HIV-related survival.”**
- **“Our findings suggest that reduced HIV foreign aid will produce modest savings to donors at the expense of HIV epidemic revival and massive loss of life among recipient nations.”**

Walensky RP, Ethan D. Borre ED, et al. Do Less Harm: Evaluating HIV Programmatic Alternatives in Response to Cutbacks in Foreign Aid. Ann Intern Med [Online]. 2017

Thank you

For latest MSF reports, go to:

www.msf.org/aids-2018,

www.msfaccess.org/stopping-deaths

sharonann.lynch@msf.org

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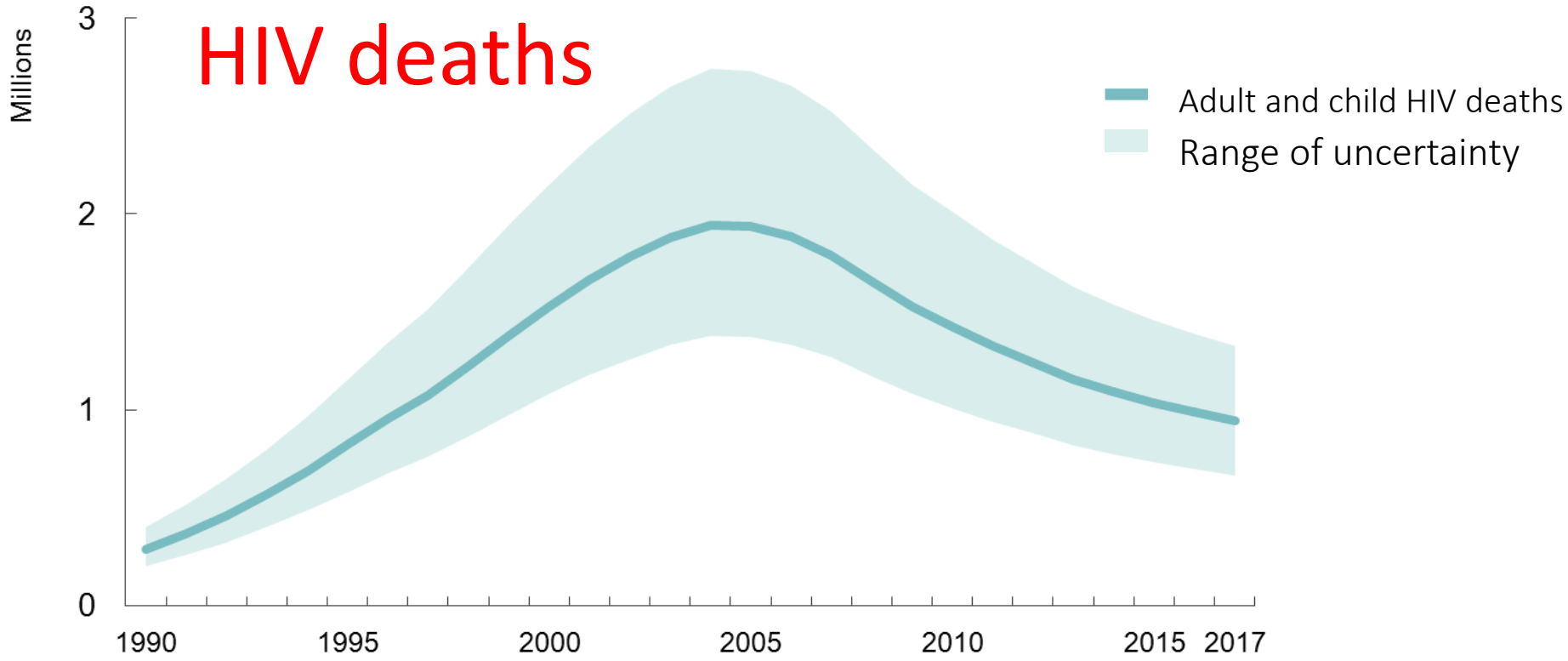
HIV deaths



2017

940,000 deaths

(670,000–1.3 mn)

1980 to 2016

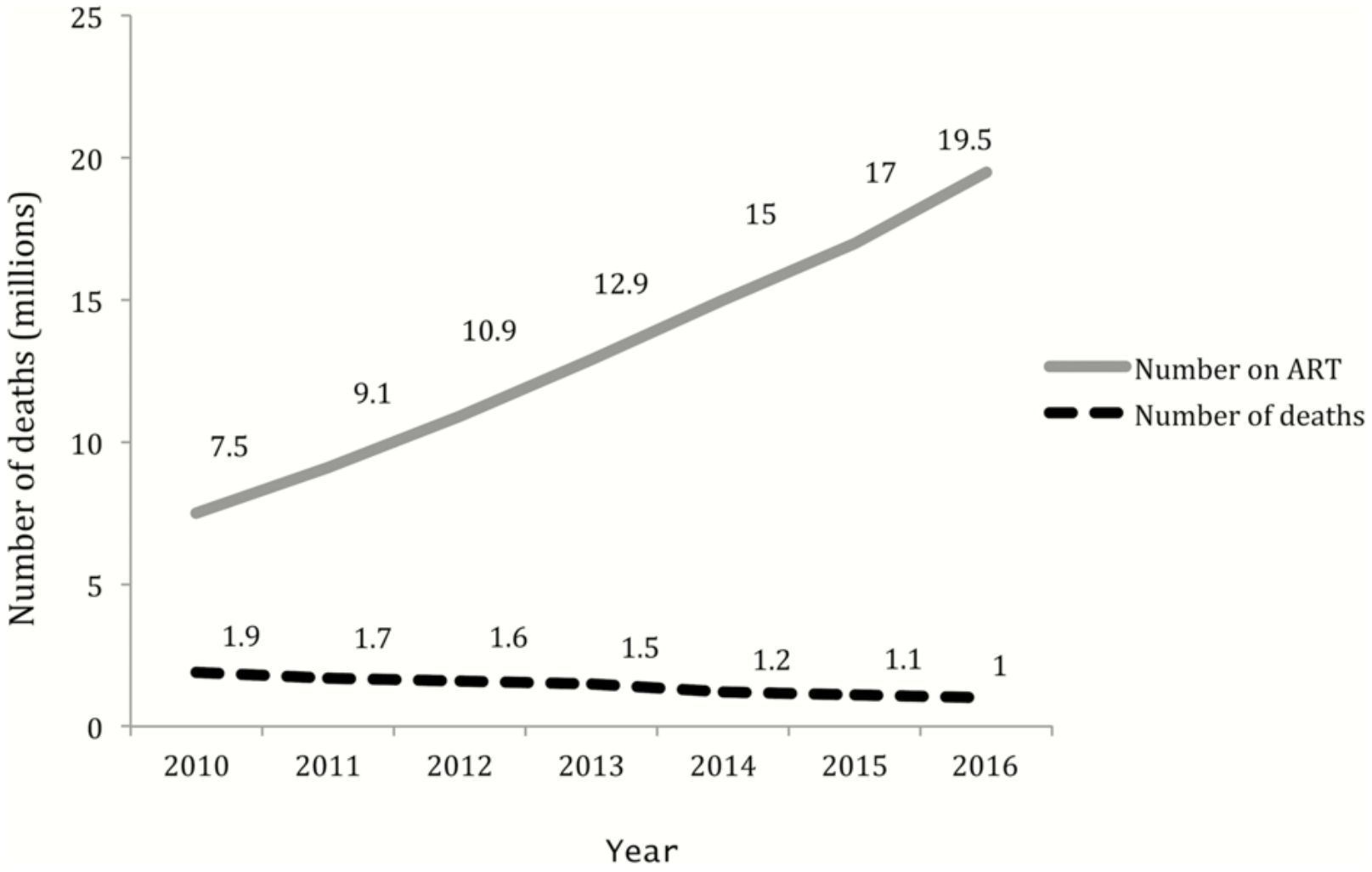
- 1980
  4,224 deaths)
- 2005
  peak at 1.91 million deaths
- 2016
  1.03 million deaths

2005 to 2016

HIV deaths decreased by 45.8%

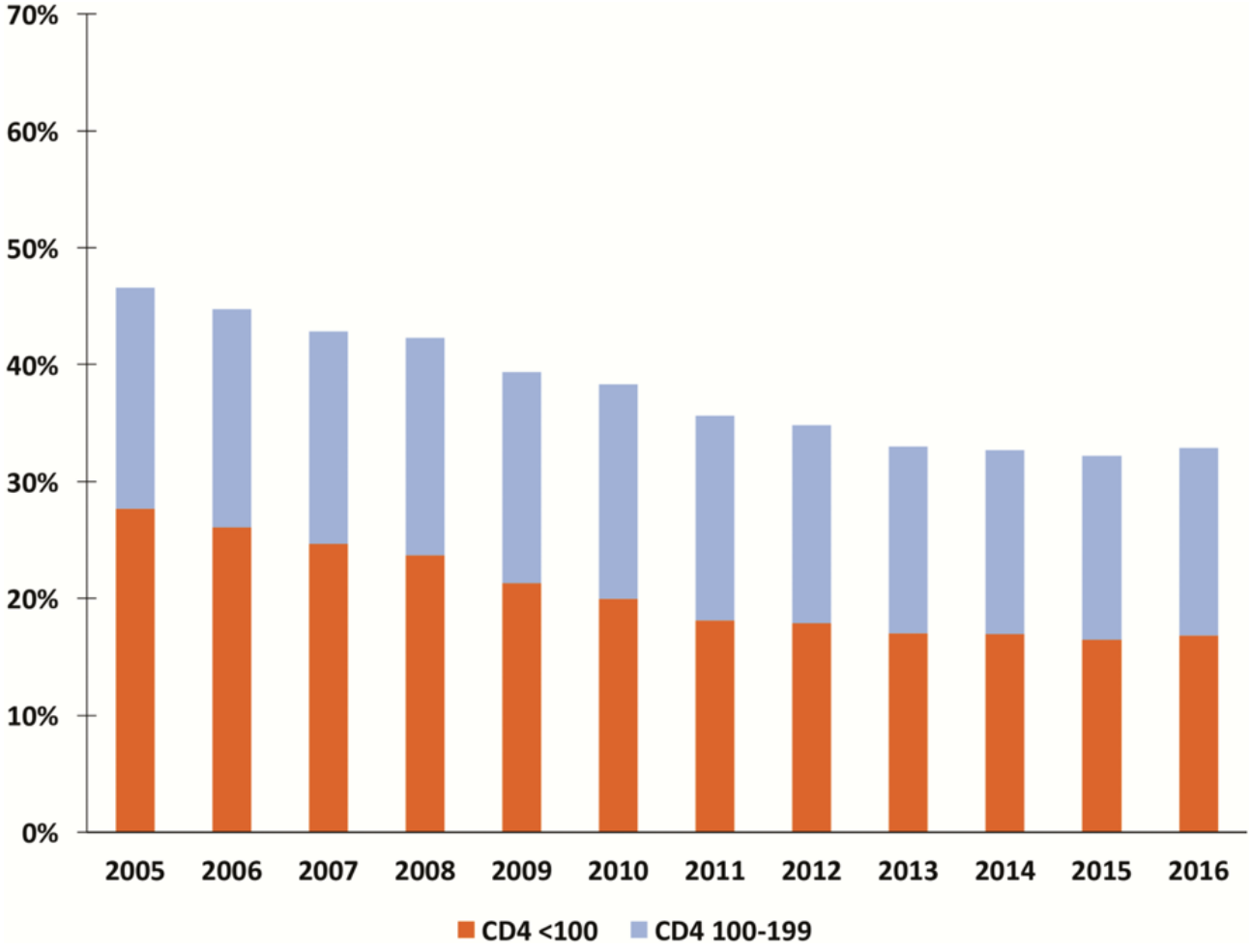
TB-related PLWHA deaths decreased 20.9%

Number of deaths as ART increases



Source: Calmy A, Ford N Meintjes G. The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. Clinical Infectious Diseases [Online]. 2018 Mar 4 [Cited 2018 Jul 15];66(Suppl 2). Available from: https://doi.org/10.1093/cid/cix1138

Low CD4 at initiation



- South Africa
- PLWHA presenting with advanced HIV disease has remained unchanged over the last 5 years
- More than a third of patients enter care with a CD4 cell count <200 cells/µL.
  - Men almost twice as likely as women (23.1% vs 12.6%) to enter care with very advanced HIV disease
- Need to support rapid identification and treatment initiation

Source: Carmona S, Bor J, Nattey C, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa's National HIV program: Data from a nationwide laboratory cohort. Clin Infect Dis [Online]. 2018 Mar 4 [Cited 2018 Jul 13];66(Suppl 2). Available from: https://academic.oup.com/cid/article/66/suppl_2/S111/4918994?searchresult=1

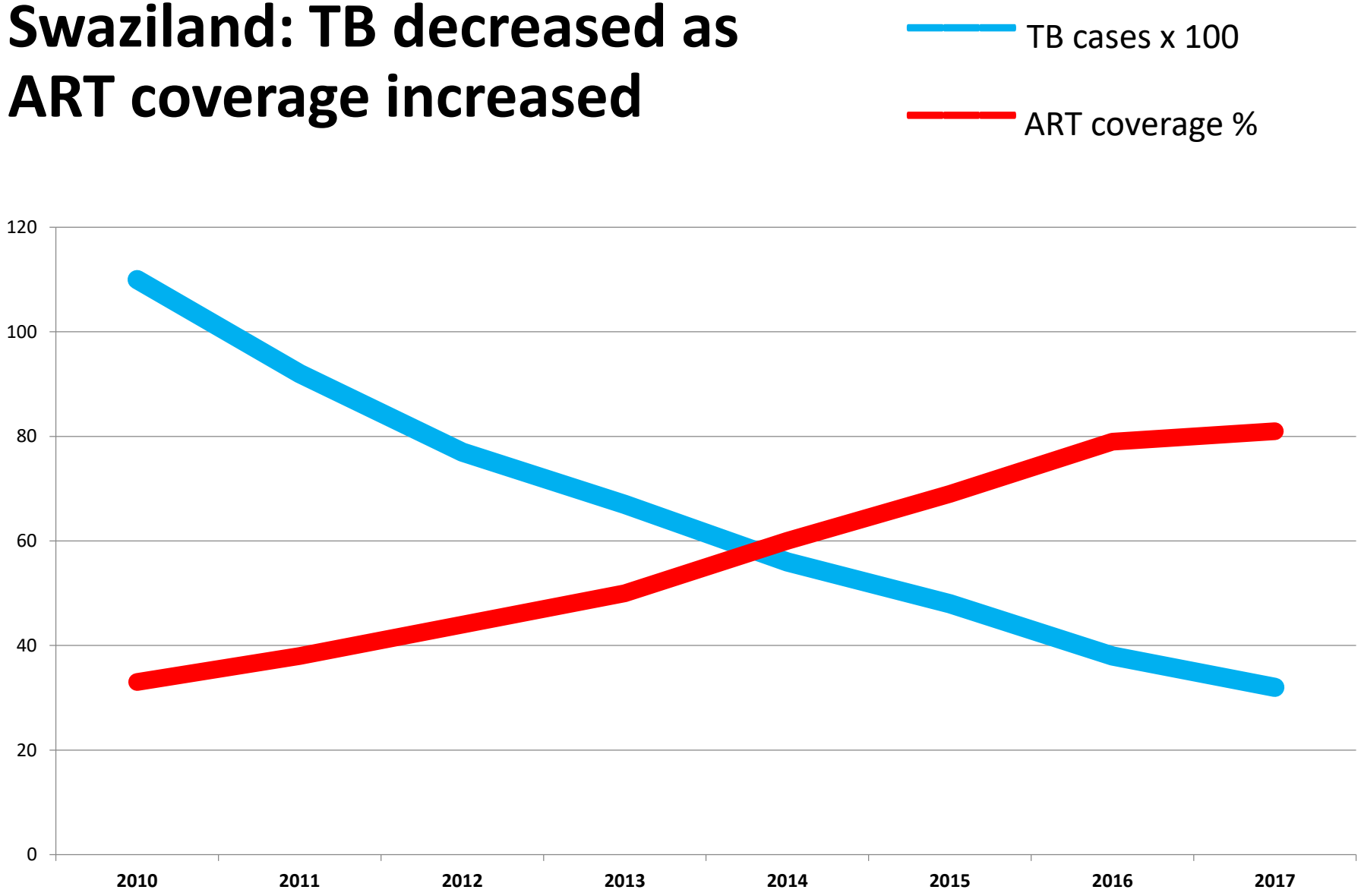
Diagnosing TB in HIV+ pregnant women

- **Symptom screening not good enough for HIV+ pregnant women**
  - **Symptom screening 90.1% sensitivity**
  - **But among HIV+ pregnant women (RSA) dropped to 28%**
- **a cluster-randomised trial to compare universal sputum TB testing with standard symptom-based testing in this population.**
- **The majority of women with previously undiagnosed prevalent TB were asymptomatic.**
- **Universal TB screening of all HIV+ pregnant women increased case detection 10-fold**
- **MGIT identified more TB than Xpert in women whose pregnancy may mask TB symptoms.**
- **Our data support sputum testing all HIV-infected pregnant women for TB in high burden**
- **Xpert detected one third the rate of TB compared with MGIT**

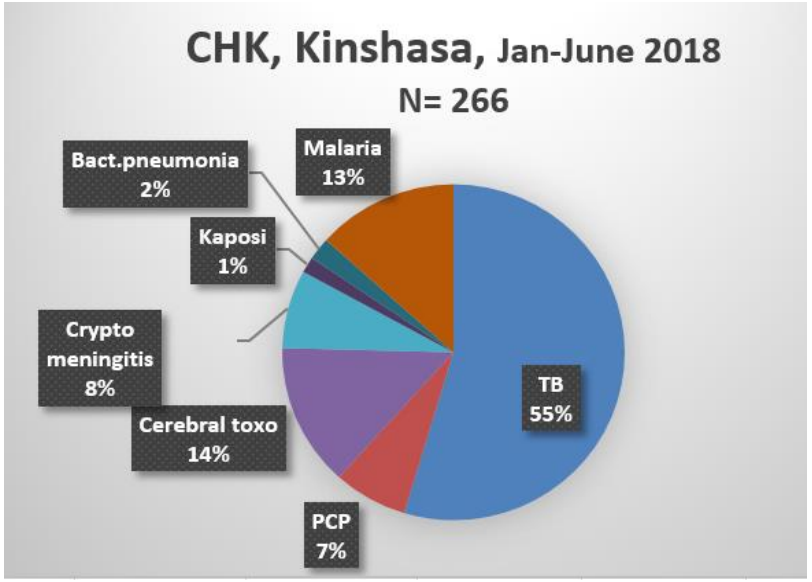
Martinson N et al. Universal sputum testing vs symptom-based testing for tuberculosis (TB) in HIV infected pregnant women: a cluster-randomised implementation trial in South Africa. 9th IAS Conference on HIV Science. 23–26 July 2017. Paris. Poster abstract TUPDB0204LB.

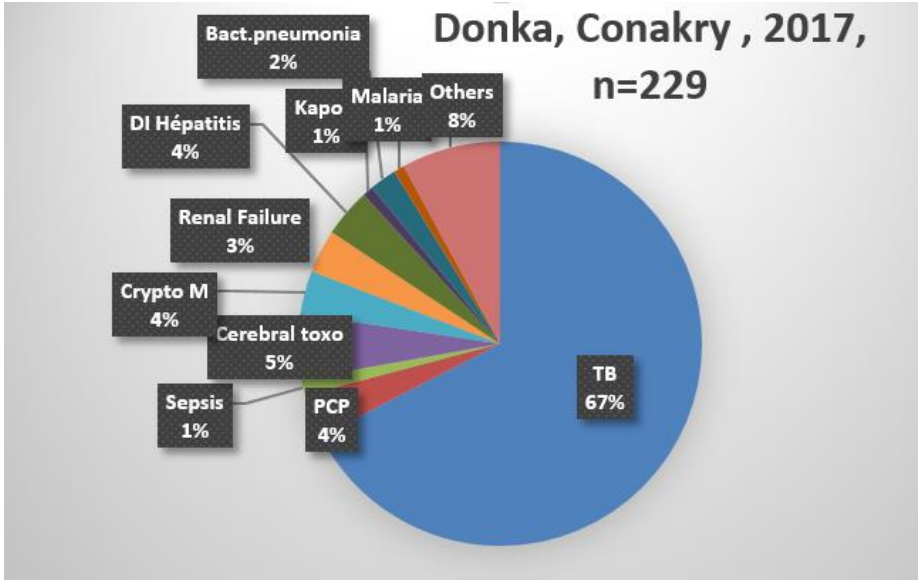
Hoffman CJ, Variava E, Rakgokong M, et al. High Prevalence of Pulmonary Tuberculosis but Low Sensitivity of Symptom Screening among HIV-Infected Pregnant Women in South Africa. PLOS ONE [Online]. 2013 Apr 17

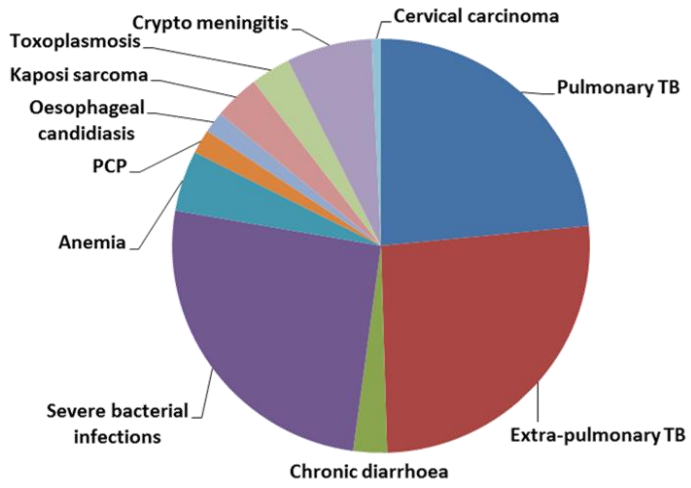
Swaziland: TB decreased as ART coverage increased



Most common causes of HIV related mortality (%) and CFR . Kinshasa, Conakry , Maputo 2018







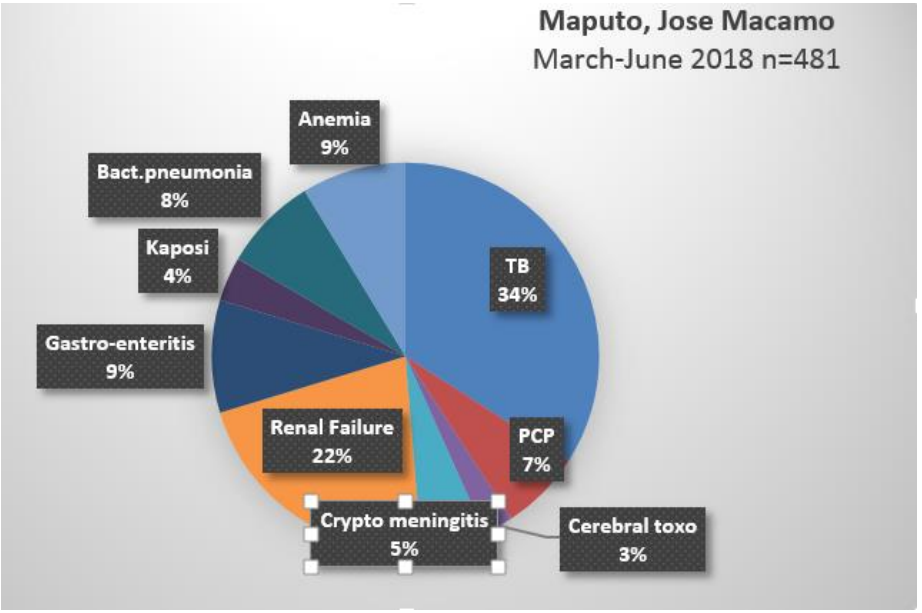


FIGURE 6.3

TB-related deaths among people living with HIV concentrated in eight countries

Distribution of tuberculosis-related deaths among people living with HIV, global, 2016