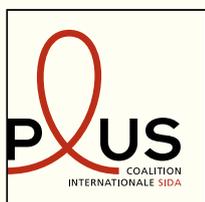


# ONE MILLION DEATHS ZERO PLAN



A GUIDE  
ON AIDS-RELATED  
MORTALITY

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# FOREWORD

Despite all the efforts aimed at ending the AIDS epidemic by 2030, we confront a paradox: those who are suffering from AIDS today seem to be ignored. Since community members and activists launched a call at AIDS 2018 for a mortality reduction plan, over 1 million people have died of AIDS. And almost 18 months later, there is still no plan.

With “One million deaths, Zero Plan”, we are not asserting that the global HIV response is ignoring mortality. The Fast-Track targets set a clear goal to reduce annual deaths below 500,000 per year by 2020. Instead, we are calling attention to the 770,000 AIDS-related deaths in 2018 and we are highlighting the lack of a response for those not reached by the 90-90-90 approach. In turn, we are demanding a more comprehensive strategy to close the gap.

In technical terms, the current 90-90-90 approach aims to minimize incidence and mortality by minimizing the number of persons living with HIV (PLHIV) who are not achieving viral suppression. The goal is to reduce the so-called “leakage” in the continuum of HIV services and thereby reduce the size of the pool of patients progressing to advanced HIV disease. This strategy makes sense, but it cannot be the exclusive focus. The lack of a complementary strategy for those reaching the pool of advanced HIV disease patients means that hundreds of thousands are left to drown every year. What lifeline for them? Access to the WHO’s recommendation for a package of care for advanced HIV disease is the clear answer. We call for a mortality reduction plan that builds on the existing 90-90-90 strategy to include a roadmap for implementation of the WHO-recommended package of care for advanced HIV disease. We call for this plan to also elaborate a framework for more robust strategic information on cases of advanced HIV disease and AIDS-related mortality.

Extraordinary progress has been made in the past decade. Since 2010, AIDS-related deaths

have fallen from 1.2 million PLHIV per year to 770,000 PLHIV per year—a 36% percent reduction in mortality that has occurred in spite of a concomitant 20% increase in the number of people living with HIV. This progress is driven by the fact that the number of PLHIV on antiretroviral therapy has more than tripled since 2010. Nevertheless, in the last ten years, over 9 million people living with HIV have died from AIDS-related causes. Moreover, progress is slowing down; the 2018 decline in annual deaths by 30,000—from 800,000 in 2017—was the smallest annual reduction since yearly mortality began to fall in 2005. If the downward trend continues at 30,000 fewer deaths per year, the 2020 targets won’t be reached until 2028.

There are tools to address the opportunistic infections that constitute the leading causes of AIDS-related mortality, they are just not being used. The current policy seems to operate under the assumption that expanding the strategy to address advanced HIV disease would slow down the effort to win the long-term battle. Yet for millions in our communities, there will be no long term, especially for the most vulnerable among in our communities who must confront AIDS without access to lifesaving medicines for the opportunistic infections that threaten lives.

This document aims to sound an alarm to communities, policymakers, and donors. It provides a primer for those seeking to understand AIDS-related mortality—the numbers, the causes, the context, the gaps in the response, and the tools we have to address it. Above all, it is a call to action.

# **GLOSSARY**

<b>AHD</b>	advanced HIV disease
<b>AMR</b>	antimicrobial resistance
<b>ART</b>	antiretroviral therapy
<b>CLHIV</b>	children living with HIV
<b>CSF</b>	cerebrospinal fluid
<b>ESA</b>	Eastern and Southern Africa
<b>PLHIV</b>	person(s) living with HIV
<b>PWID</b>	people who inject drugs
<b>LMIC</b>	low-and middle-income countries
<b>MSM</b>	men who have sex with men
<b>OI</b>	opportunistic infection
<b>WCA</b>	West and Central Africa
<b>WHO</b>	World Health Organization

# TABLE OF CONTENTS

## I.

### MORTALITY BY THE NUMBERS

- # 8 Global progress is not only far from targets, it's slowing down
- # 9 Global progress masks very different regional trajectories

## II.

### 90-90-90 AS A MORTALITY REDUCTION STRATEGY

- # 10 The logic of 90-90-90's impact on mortality
- # 10 The strategy's built-in gap
- # 11 On track to end AIDS?  
Half are on track to develop AIDS
- # 11 The existing gaps

## III.

### THE MANY PATHS TO AIDS-RELATED MORTALITY

- # 12 All pass through advanced HIV disease
- # 13 Major Opportunistic Infections of Advanced HIV Disease
- # 15 Interventions for advanced hiv disease
- # 16 The paths to advanced HIV disease
- # 17 Real-world data on treatment-experienced PLHIV and advanced HIV disease

## IV.

### MEASUREMENTS OF MORTALITY: MORE QUESTIONS THAN ANSWERS

- # 18 A missing piece of the puzzle: the lost-to-follow-up cohort
- # 19 A missing piece of the puzzle: mortality in key populations
- # 20 Lots of questions, not enough data to answer them

## V.

### MORTALITY IN THE CONTEXT OF THE HIV CONTINUUM FRAMEWORK

- Reinforcement of HIV Continuum Pillars as Catalyst to Reducing Mortality
- # 21 Communities' key role in strengthening the HIV Continuum
- High mortality of PLHIV with AHD in the 90 day period after ART initiation
- # 23 Missing pillars in the HIV Continuum

## VI.

### WHO'S RECOMMENDATIONS FOR ADVANCED HIV DISEASE

- # 24 Components of who-recommended package of care interventions for advanced hiv disease
- # 25 Barriers to Uptake of the AHD Package of Care

## VII.

### # 26 EXAMINING COMMON MISCONCEPTIONS

## VIII.

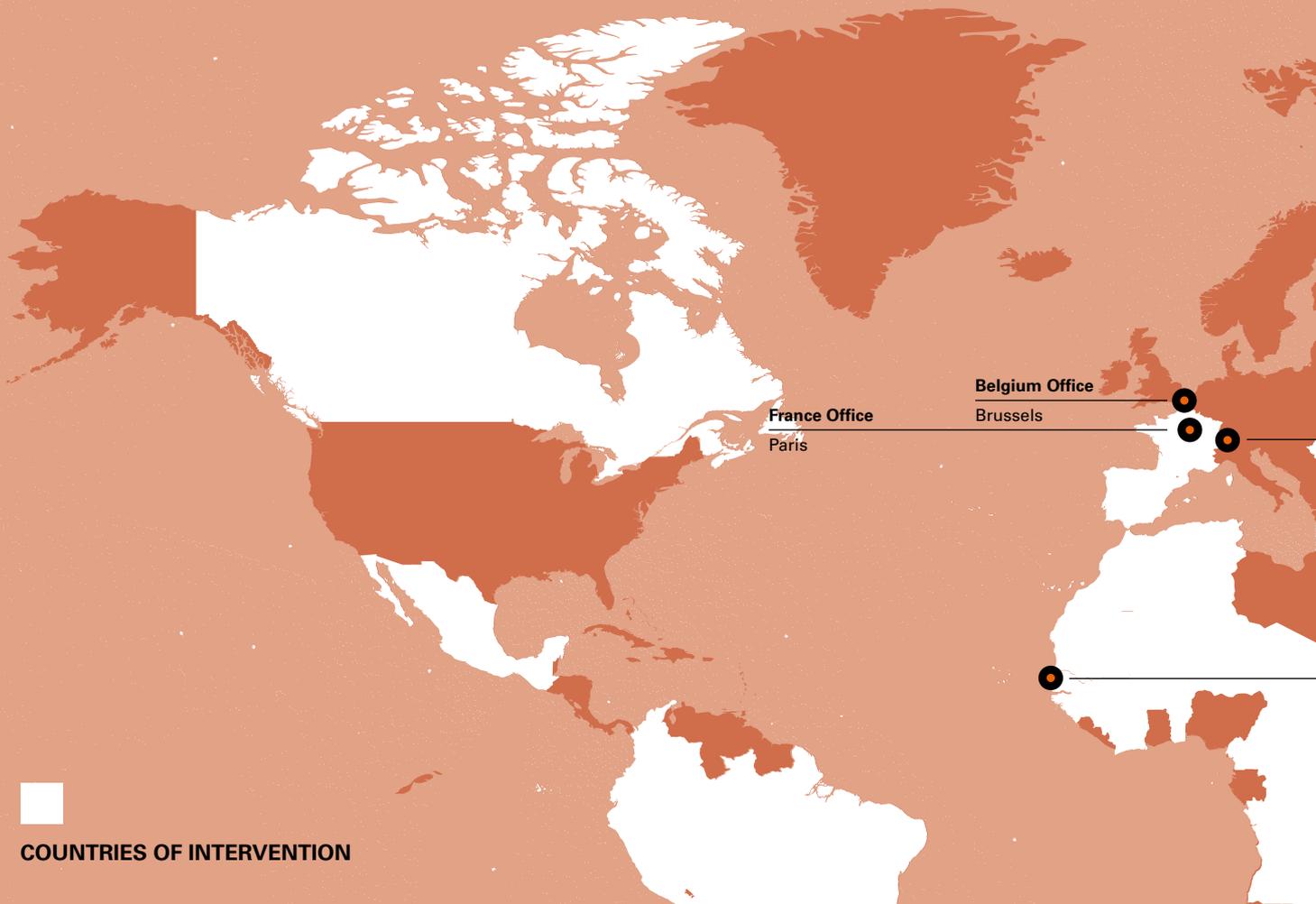
### # 28 A CALL TO ACTION

## IX.

### # 29 REFERENCES

## X.

### # 31 ANNEX: RESOURCES FOR FURTHER EXPLORATION OF ADVANCED HIV DISEASE



**COUNTRIES OF INTERVENTION**

**MEMBER ORGANIZATIONS**

**OFFICES**

**AIDES**  
France

**ARAS**  
Romania

**GAT**  
Portugal

**REVS PLUS**  
Burkina Faso

**FRANCE**  
Paris

**ALCS**  
Morocco

**ARCAD-SIDA**  
Mali

**GROUPE  
SIDA GENÈVE**  
Switzerland

**CO «100% LIFE»**  
Ukraine

**BELGIUM**  
Brussels

**ANCS**  
Senegal

**COCQ-SIDA**  
Quebec

**KIMIRINA**  
Ecuador

**MALAYSIAN  
AIDS COUNCIL**  
Malaysia

**SWITZERLAND**  
Geneva

**ANSS**  
Burundi

**IDH**  
Bolivia

**PILS**  
Mauritius

**HUESPED FUNDATION**  
Argentina

**AFRICA**  
Dakar

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# COALITION PLUS'

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## NETWORK IN 2019

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An international union of community-based NGOs in the fight against AIDS and viral hepatitis founded in 2008, Coalition PLUS now operates in 52 countries and works with some one hundred civil society organizations. In line with its community-based approach, our coalition advocates for the expertise of people infected with, affected by or particularly vulnerable to HIV and viral hepatitis to be fully recognized and for the systematic involvement of their communities in the decision-making process and the development and implementation of health programs that affect them. Acting according to a principle of shared governance, it involves 16 member organizations from the Global North and Global South in its strategic decision-making. Through the programs of its Secretariat and its different geographic, thematic and linguistic networks, it aims to strengthen the capacity of community-based associations and create forums for the sharing of knowledge and expertise.



**Switzerland Office**

Geneva

**Africa Office**

Dakar

**NETWORKS**

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**AGCS PLUS  
RIGHT PLUS  
LUSOPHONE NETWORK  
MENA PLATFORM  
WEST AFRICA PLATFORM  
CENTRAL AND EASTERN AFRICA PLATFORM  
INDIAN OCEAN PLATFORM  
AMERICAS-CARIBBEAN PLATFORM  
EUROPE PLATFORM**

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# I.

## MORTALITY

### BY THE NUMBERS

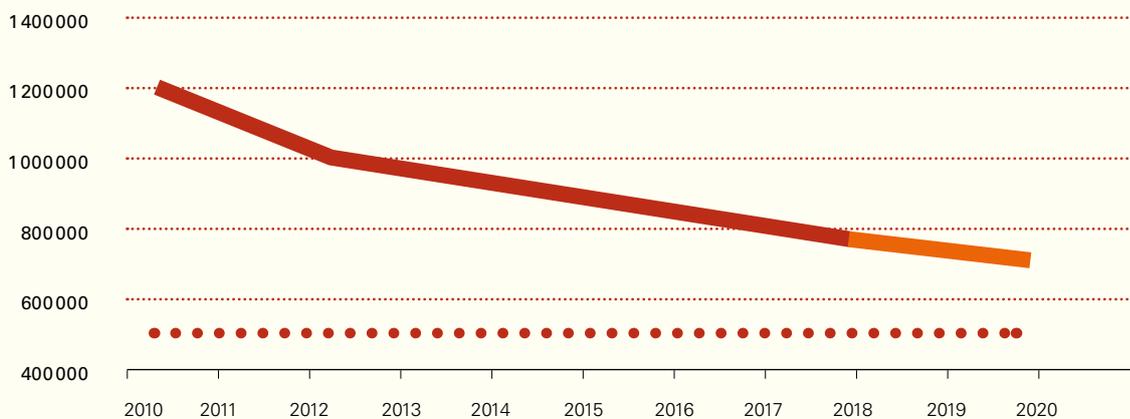
#### GLOBAL PROGRESS IS NOT ONLY FAR FROM TARGETS, IT'S SLOWING DOWN

There has been progress. UNAIDS estimates that annual deaths have fallen from 1.2 million in 2010 to 770,000 in 2018 (a 36% reduction). This comes despite an increase of total PLHIV from 31.7 million to 37.9 million (a 20% increase). More people are living with HIV, while fewer PLHIV are dying from AIDS than any year since 1995. This progress can be explained by the impact of the scale up of the number of PLHIV on ART and the expansion of early

ART initiation. Nevertheless, in the last ten years, over 9 million people living with HIV have died from AIDS-related causes. Even more concerning, **progress is slowing down. Last year represented the lowest decrease since the decline in annual deaths started in 2005**—from 800,000 deaths in 2017 to 770,000 in 2018. If the current trajectory of 30,000 annual reduction continues, we would only reach the 2020 targets in 2028. In the decade until 2028, the current trajectory means nearly 6 million PLHIV would die of AIDS-related causes. Despite progress, we are way off target.

#### GLOBAL AIDS-RELATED MORTALITY

■ 2010–2018 | ■ Current Trajectory | ●●● 2020 Mortality Target



Source: UNAIDS 2019 Data Report

#### FAST-TRACK TARGETS:

Reduce global HIV-related deaths to below 500 000 per year by 2020

Reduce global HIV-related deaths to below 200 000 per year by 2030

#### REALITY:

**Progress is slowing down:** The 30,000 drop from 2017 (800,000) to 2018 (770,000) marked the lowest annual reduction in deaths since the peak in 2004;

**We are way off track:** If progress does not continue to slow, we will reach 2020 targets of 500,000 by 2028;

## GLOBAL PROGRESS MASKS VERY DIFFERENT REGIONAL TRAJECTORIES

Total mortality has declined by 430,000 annual deaths since 2010, from 1.2 million AIDS-related deaths per year to 770,000 in 2018. But progress has not been even across the globe. Eastern and Southern Africa accounted for more than half of this decline, with annual mortality falling by 240,000 AIDS-related deaths per year since 2010. Significant global declines mask less impressive progress elsewhere. In fact, annual mortality

has increased by 9% in Middle East / North Africa since 2010 ( from 7,700 to 8,400); in the same period, AIDS-related deaths per year have also increased by 6% in Eastern Europe Central Asia (from 36,000 to 38,000).

### AIDS-RELATED DEATHS BY REGION <sup>1</sup>

UNAIDS REGION	2010 MORTALITY	2018 MORTALITY	REGIONAL CHANGE (by number of deaths)	REGIONAL CHANGE (by percentage)
Eastern and Southern Africa	550,000	310,000	- 240,000	- 44%
West and Central Africa	230,000	160,000	-70,000	-30%
Asia and Pacific	270,000	200,000	-70,000	-26%
Western/Central Europe and North America	19,000	13,000	- 6,000	- 32%
Latin America	40,000	35,000	- 5,000	- 13%
Caribbean	11,000	6,700	- 4,300	- 39%
Middle East and North Africa	7,700	8,400	+ 700	+ 9%
Eastern Europe and Central Asia	36,000	38,000	+ 2,000	+ 6%

NOTE: The regional sums from 2010 and 2018 are 1,163,700 and 771,000 respectively. These numbers differ slightly from the same UNAIDS website's global estimates of 1.2 million and 770,000.

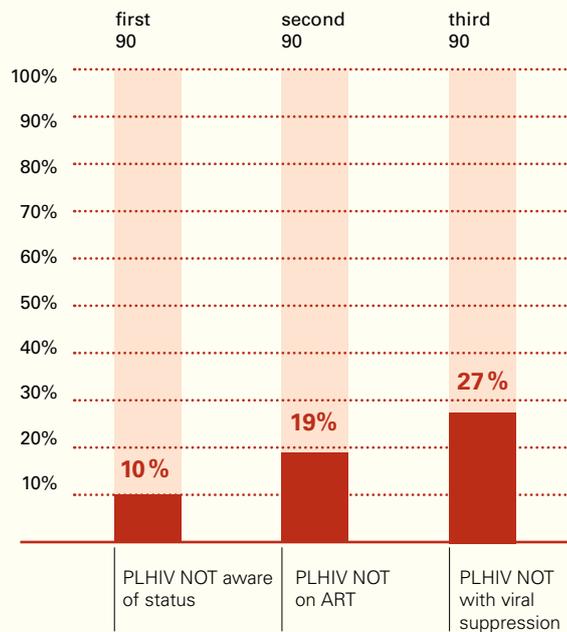
## II.

# 90-90-90 AS A MORTALITY REDUCTION STRATEGY

### THE LOGIC OF 90-90-90'S IMPACT ON MORTALITY

In 2014, the Fast Track Targets of 90-90-90 were set for 2020<sup>2</sup>. The objective aims at: 90% of people living with HIV aware of their status; 90% of people who know their status on ART; and 90% of people on treatment with a suppressed viral load. The Fast Track Targets also set an objective of less than 500,000 annual AIDS-related deaths by 2020. The two are linked. 90-90-90's cumulative goal to maximize the number of PLHIV on the track to viral suppression is a strategy to divert people off the track to AIDS. More broadly, the focus on viral suppression makes sense because it is key to the achievement of the HIV response's ultimate objectives: 1) a reduction of incidence (because viral suppression means undetectable, and undetectable = untransmissible); 2) a reduction in mortality (because viral suppression has been demonstrated to drastically lower the risk of AIDS-related deaths in PLHIV). The logic is sound; the emphasis on 90-90-90 as a catalyst of mortality reduction makes sense. Yet this strategy also comes with a major built-in gap.

### THE STRATEGY'S BUILT-IN GAP



10-19-27 CASCADE (90-90-90 INVERTED)

As illustrated by the graph above, simple math shows us that the achievement of 90-90-90 would mean that over 25% of the PLHIV population has not achieved viral suppression. This becomes more obvious if the 90-90-90 cascade is presented as the **10-19-27 cascade**: **10% of PLHIV are not aware of their status, 19% of PLHIV are not on ART, and 27% of PLHIV are not virally suppressed.** These figures means that 1 in 4 PLHIV would remain at risk of transmission to others and at risk of progressing to advanced HIV disease. Furthermore, if a disproportionate percentage of this 1 in 4 are from key populations, then the public health risks resulting from the marginalization of these populations ensure they will continue to contribute disproportionately to HIV incidence and mortality. As often-margi-

nalized groups at the center of the dynamic epidemic, viral suppression in key populations is not only essential to reaching the Fast Track Targets, it is essential to SGD goals on health (SDG 3) and reduced inequalities (SDG 10).

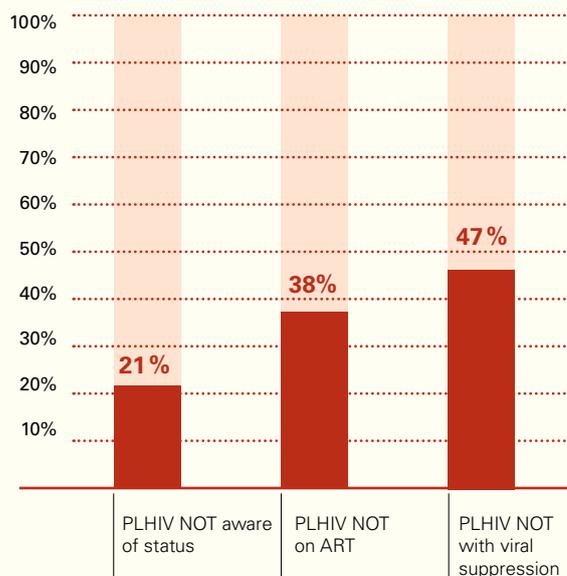
Yet more sobering, if 1 in 4 PLHIV would not be virally suppressed in this ideal scenario, one year out from the 2020 targets we remain far from the ideal.

**ON TRACK TO END AIDS? NEARLY HALF OF GLOBAL PLHIV ON TRACK TO DEVELOP AIDS**

The 2018 global 90-90-90 figures may seem promising at first: 79-78-87<sup>3</sup>. Yet the math proves more sobering. When we apply the 10-19-27 cascade to the actual global cascade, we get: 21-38-47.

- **21% of the global PLHIV population do not even know they are living with HIV**
- **38% of the global PLHIV population are not on ART; 21% of the PLHIV population that don't know their status plus the 17% aware of status and not on treatment**
- **47% of the global PLHIV population have not achieved viral suppression; 38% of the PLHIV population not on ART plus the 9% of PLHIV on ART but not achieving viral suppression**

**THE EXISTING GAPS**



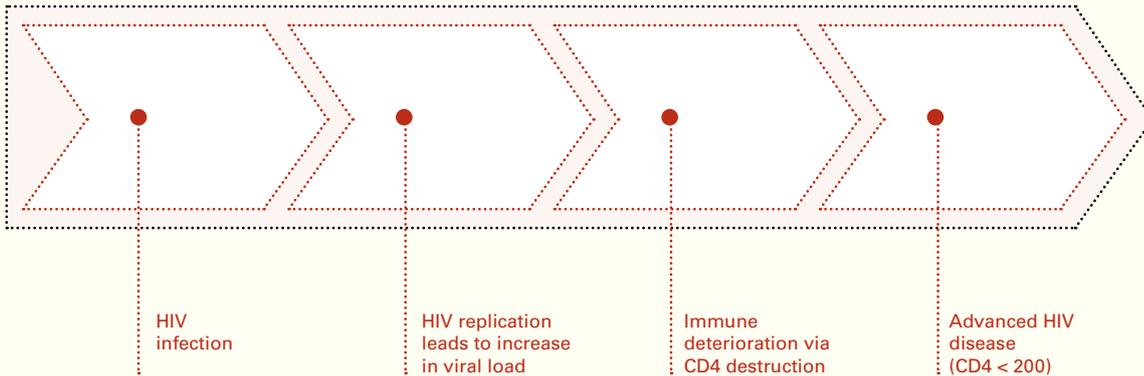
**THE 21-38-47 GLOBAL CASCADE (OR 79-78-87 UNDER 90-90-90)**

In other words, in an era where effective prevention and treatment interventions exist, **17.6 million PLHIV are currently at direct risk of advanced HIV disease and transmission to partners** — i.e. as a result of not achieving viral suppression. Put another way, 47% of PLHIV are not able to enjoy the benefits of the fact that undetectable = untransmittable. Moreover, **even if 90-90-90 had been achieved by today, over 10 million current PLHIV would still remain on a path to possible AIDS-related mortality.**

# III.

## THE MANY PATHS TO AIDS-RELATED MORTALITY

ALL PASS THROUGH ADVANCED HIV DISEASE



### HIV PROGRESSION IN THE ABSENCE OF ART

Once HIV has entered the body, it begins to replicate. HIV replicates inside CD4 cells, a key defense of the immune system. The process of HIV replication can eventually destroy a host CD4 cell. If viral suppression is not achieved, the virus replication process

will eventually begin to destroy CD4 cells faster than the immune system can regenerate CD4 cells, leading to the steady erosion of the immune system and ultimately to advanced HIV disease.

In the absence of ART, the speed of progression to advanced HIV disease in an individual PLHIV will vary. UNAIDS estimates that, without initiation of ART, the average adult case of HIV progresses from infection to advanced HIV disease in 10-15 years<sup>4</sup>. However, some individuals living with HIV may experience

more accelerated immune suppression within only a matter of years, while others may take longer than 15 years. Moreover, immune suppression in young children is particularly accelerated, which is why WHO defines all children under 5 years old living with HIV as having advanced HIV disease.

The term *advanced HIV* disease has taken on increasing prominence in technical discussions. Loosely speaking, advanced HIV disease has replaced the stage of HIV immune suppression that has historically been referred to as AIDS. The WHO defines advanced HIV disease as:

.....

Why the threshold of 200 CD4? Because beyond this point of immune suppression PLHIV become increasingly vulnerable to opportunistic infections (OI). Each of the major OIs can be targeted by interventions in the WHO's recommendations for an advanced HIV disease package of care (elaborated on page 24).

**For adults and adolescents, and children  $\geq 5$  years old**, advanced HIV disease is defined as the presence of a CD4 cell count  $< 200$  cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event.

.....

**All children  $< 5$  years old** with HIV infection are considered as having advanced HIV disease.

.....

## THE MAJOR OPPORTUNISTIC INFECTIONS OF ADVANCED HIV DISEASE

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### ● TUBERCULOSIS (TB):

.....

Tuberculosis is a bacterial infection that represents the leading cause of mortality in PLHIV. In 2018, there were an estimated 251,000 TB deaths from 862,000 total new TB cases in PLHIV. TB commonly attacks the lungs, though it can affect any organ—people with HIV are more likely to have TB outside of the lungs (extrapulmonary TB). TB can manifest/present as latent TB infection (LTBI) and active TB. If not treated when at the latent stage, the infection may progress to active TB—a symptomatic and potentially contagious phase of the infection. PLHIV face an extremely elevated risk (vis-à-vis non-PLHIV) of their infection progressing to active TB<sup>5</sup>. TB preventive therapy is recommended by WHO

for all people living with HIV in whom active TB has been ruled out. Drug-susceptible cases of active TB can be cured with very high rates of efficacy when medicines are provided and taken properly. When key drugs are not effective against active TB, these cases are known as drug-resistant TB; if the two most powerful drugs are not effective, such cases are known as multi-drug resistant TB. New and repurposed drugs—bedaquiline, linezolid, clofazimine, delamanid and in some case of extreme drug-resistance, pretomanid—have shown to improve treatment efficacy or safety for drug-resistant cases. . If not effectively treated, active TB poses a high risk of mortality.

● CRYPTOCOCCAL MENINGITIS (CM):

---

Under conditions of immune suppression, this opportunistic (fungal) infection can disseminate to the central nervous system. CM is estimated to be the second leading cause of AIDS-related mortality, with estimates of 223,100 cases per year and 181,000 deaths<sup>6</sup>. Cryptococcal meningitis (as well as a precursor condition known as

cryptococcal antigenaemia) can be diagnosed with an affordable rapid diagnostic test, a cryptococcal antigen lateral flow assay known as a CrAg test. Cryptococcal meningitis is fatal if not treated. Treatment with the preferred WHO-recommended regimen was found to reduce mortality in a clinical trial to as low as 24% at 10 weeks.

● PNEUMOCYSTOSIS JIROVECI PNEUMONIA (ALSO KNOWN AS PJP OR PCP):

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Pneumocystis pneumonia is a fungal infection that attacks the lungs. An estimated 400,000 cases of PJP/PCP occur annually in PLHIV with AHD<sup>7</sup>. PJP/PCP is difficult to

diagnose in LMICs, a barrier that contributes to limited appreciation of the disease burden.

● TOXOPLASMOSIS:

---

Toxoplasmosis is a protozoan infection acquired from food or environmental exposure. Under severe immune suppression, active infection can lead to a high risk of

mortality. Toxoplasmosis is difficult to diagnose in LMIC settings, a barrier that contributes to limited appreciation of the disease burden.

● SEVERE BACTERIAL INFECTIONS (SBI):

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Many non-TB bacterial infections can pose substantial risk to PLHIV with advanced HIV disease. The most common of these pathogens have names well-known to the general public: *Strep pneumoniae*, non-typhoidal *Salmonella*, *E. coli*, and *Staph aureus*. Collectively, they are esti-

mated to account for nearly 1/3 of AHD hospital admissions<sup>8</sup>. Moreover, current trends of increasing antimicrobial resistance (AMR) exacerbate the risk of AIDS-related mortality from SBI and represent an important example of the public health threat of AMR to PLHIV.

## INTERVENTIONS FOR ADVANCED HIV DISEASE

In combination with the re-initiation of ART, specific interventions for these OIs can have a major impact on the reduction of incidence of OIs and the reduction of mortality of PLHIV suffering from OIs. A scheme of the WHO's package of care is elaborated later in the document. Below is a brief summary of some of the key commodities for addressing the leading causes of AIDS-related mortality.

### KEY COMMODITIES FOR ADVANCED HIV DISEASE

DISEASE	COMMODITIES
Advanced HIV disease	CD4 test
Latent TB Infection	Latent TB infection (LTBI) treatment : rifapentine-based therapy (3HP**/1HP), isoniazid preventive therapy (IPT) for 6-36 months; rifampicin plus isoniazid for three months (3HR); 4 months of rifampicin alone <sup>9</sup>
Active Tuberculosis Infection	Xpert MTB/RIF (Ultra) for diagnosis of active TB:  and  LF-LAM for diagnosis of active TB in any inpatient PLHIV with signs/symptoms of TB, or with advanced HIV or who are seriously ill; Diagnosis of outpatient PLHIV with signs and symptoms of TB or seriously ill, or with CD4 < 100 <sup>10</sup>  Treatment for drug-susceptible active TB : 2HRZE/4HR <sup>5</sup> (For more information on treatment of drug-resistant active TB, see WHO's consolidated 2019 guidelines on drug-resistant TB)
Cryptococcal antigenaemia (present only in blood)	Rapid diagnostic: CrAg Test (point-of-care later flow assay in blood) Pre-emptive treatment: Fluconazole
Cryptococcal meningitis (present also in CSF)	Rapid diagnostic: CrAg Test (point-of-care later flow assay in cerebrospinal fluid (CSF)) Preferred treatment: Flucytosine + Amphotericin B Alternative treatment: Flucytosine + Fluconazole
Toxoplasmosis Pneumocystis pneumonia (PJP/PCP)	Prophylaxis: Co-trimoxazole* <sup>^</sup> Treatment (for PJP/PCP and as alternative preferred for toxoplasmosis) <sup>#</sup> : High dose co-trimoxazole

\*\* HP is a short-course regimen that combines two antibiotics active against TB, isoniazid and rifapentine. 1HP denotes a regimen of isoniazid/rifapentine taken daily for four weeks (1 month). 3HP denotes a regimen of isoniazid/rifapentine taken once a week for 12 weeks (3 months).

\*\*\* RH is a short-course regimen that combines two antibiotics active against TB, isoniazid and rifampin. 3RH denotes a regimen taken once daily, for 12 weeks (3 months).

\* Q-TIB : a fixed-dose combination of co-trimoxazole, isoniazid, and vitamin B6.

<sup>^</sup> Co-trimoxazole is itself a combination of trimethoprim and sulfamethoxazole.

<sup>#</sup> The primary treatment for toxoplasmosis—sulphadiazine + pyrimethamine—is widely unavailable in LMICs where need is greatest.

<sup>§</sup> 2HRZE/4HE; 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E); followed by 4 months of HE

## THE PATHS TO AHD

PLHIV paths to AHD can be categorized in three ways:

- treatment-naïve PLHIV (never on ART)
- treatment-experienced PLHIV (previously initiated on ART but not currently on ART)
- treatment-experienced PLHIV (currently on ART)

### TREATMENT-NAÏVE:

#### Never diagnosed:

Some PLHIV may progress to advanced HIV disease and subsequently die without ever being diagnosed with HIV. Misreporting or non-reporting on the underlying cause-of-

death in many LMICs can make it difficult to collect good data on the relative size of this population, especially where many of these individuals die outside of health facility settings.

#### Late diagnosis:

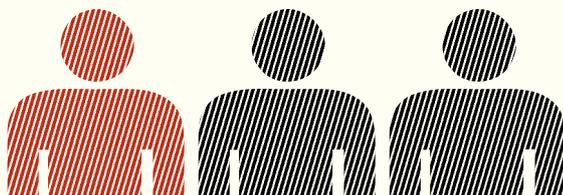
Many PLHIV will be diagnosed with HIV only after progressing to advanced HIV disease, often receiving their HIV diagnosis when presenting to care for an opportunistic infection. The WHO estimates that nearly 1 in 3 PLHIV initiating ART have advanced

HIV disease<sup>11</sup>. This figure rises to 50% of newly diagnosed male PLHIV in LMICs. It is not clear what percentage of these late diagnoses come as a direct result of presentation at a health facility with an opportunistic infection.

#### Loss in referral:

Some PLHIV are tested but either not informed of their status or not linked to care. These PLHIV face a substantial risk of progressing to AHD. Where marginalized populations face systemic barriers that contribute to unsuccessful communication of status or linkage to care, their HIV-related risks are exacerbated if they face similar barriers to accessing health

services in the event that they later develop advanced HIV disease. While we know that 1/3 of those newly diagnosed with HIV have AHD, it is not clear what percentage of non-diagnosed PLHIV have AHD, nor is it clear what percentage of those lost to referral are living with AHD.



**ONE IN THREE PEOPLE STARTING  
TREATMENT FOR HIV  
HAVE ADVANCED DISEASE.**

● TREATMENT-EXPERIENCED (BUT NOT CURRENTLY ON ART)

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**Treatment interruption:**

PLHIV may start ART and subsequently discontinue. This can lead to risk of progression to AHD. Treatment interruption may occur for a wide array of reasons and their examination remains beyond the scope of this document. However, it is worth noting that there

is limited robust data on the percentage of advanced HIV disease and AIDS-related mortality that is linked to PLHIV treatment interruption. Moreover, estimations of the size of this population are highly subject to assumptions about mortality in individuals lost to follow up.

● TREATMENT EXPERIENCED (AND CURRENTLY ON ART)

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**Treatment failure:**

PLHIV may be adherent to their ART but nevertheless fail their regimen. Treatment failure is due to transmitted or acquired resistance. If

resistance is not identified and/or alternative regimens are not available, these individuals will eventually progress on the path to AHD.

**Reconstitution (immune recovery):**

PLHIV facing AHD may remain at risk in a window following ART initiation / re-initiation ; the duration of the window of time to immune recovery depends on several factors, including the baseline CD4 at time of treat-

ment initiation; in the period that the immune system rebounds, PLHIV continue to face risks of opportunistic infection; in addition to the direct threat from opportunistic infections.<sup>12</sup>

**Reconstitution failure:**

PLHIV may initiate treatment at the stage of advanced HIV disease and, despite reaching viral suppression, experience prolonged sub-optimal immune reconstitution; approximately

20% of severely immune suppressed PLHIV initiating or re-initiating ART will experience reconstitution failure.<sup>13</sup>

**REAL-WORLD DATA: TREATMENT-EXPERIENCED CONTRIBUTE AN IMPORTANT SHARE OF THOSE REACHING AHD**

Some natural questions stemming from the above schema would be: what is the distribution of PLHIV with AHD across each group? How many PLHIV ultimately reach AHD per year? And what percentage of PLHIV reaching AHD are dying and what percentage are recovering? The short answer, there is not robust data. However, there is data that suggests that treatment-experienced PLHIV constitute an important share of PLHIV suffering from AHD.

Across four MSF-supported hospitals in four separate sub-Saharan African countries, an evaluation of patients admitted with advanced HIV disease showed that well over half of all patients admitted with AHD were treatment experienced<sup>14</sup>. In all four settings, those on ART for more than 6 months constituted the biggest share of admitted patients (versus treatment naïve or those on ART for less than 6 months).

# IV.

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## MEASUREMENTS

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### OF MORTALITY: MORE

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### QUESTIONS THAN ANSWERS

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#### MISSING PIECES OF THE PUZZLE: LOSS TO FOLLOW UP

At present, several seemingly straightforward questions lack clear answers. These include: how many individuals are reaching AHD annually? What percentage of those with AHD are dying and what percentage are recovering? This gap in the epidemiological puzzle is so challenging because one major piece is missing: the profile of PLHIV in the lost-to-follow up population. One reason this profile is so hard to identify is because it is dynamic: in the PLHIV population counted as lost to follow up, some percentage have died. But that percentage is often not known. Limited data on the lost-to-follow-up profile of a PLHIV cohort is not only problematic for calculating AHD numbers, it is a key barrier to accurately calculating overall AIDS-related mortality. This point was illustrated by a recent study<sup>15</sup> evaluating mortality in four Zambian provinces, where underestimation of death in lost-to-follow up led researchers to conclude that official projections of overall mortality in the study area were drastically underestimated.

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#### ● ZAMBIA: OFFICIAL MORTALITY ESTIMATES UNDER THE MICROSCOPE<sup>16</sup>

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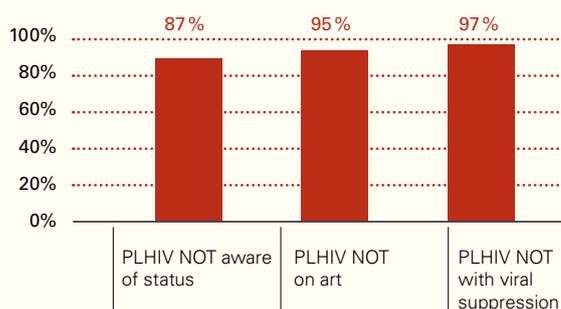
To validate official projections of local mortality in PLHIV initiating ART in 4 provinces in Zambia, a study was conducted that traced the vital status of treatment-experienced PLHIV who were lost to follow up. Through a methodology that rigorously explored the health status of a random sample of 10% of all individuals classified as treatment-experienced and subsequently lost-to-follow up, the research identified a significantly higher mortality rate than previously estimated. When the assumption for death in the lost-to-follow-up cohort was corrected, the new overall 2-year mortality rate for PLHIV initiating treatment in the region was increased three-fold. Where the official statistics had estimated 3,144 deaths, the study suggested 11,582 deaths. The study was published in January 2018. Curiously, despite this data, the subsequent UNAIDS report actually reduced the estimated mortality in Zambia over the period examined by the study.<sup>17</sup>

## MISSING PIECES OF THE PUZZLE: MORTALITY IN KEY POPULATIONS

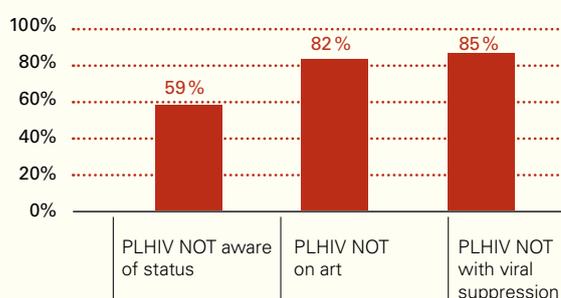
Beyond the challenge of bad data, there is also the challenge of limited data. While UNAIDS provides robust data highlighting that a disproportionate share of new infections occurs in key populations, limited data could be found on 90-90-90 or mortality in key populations. We know that in all regions except Eastern / Southern Africa and the Caribbean, key populations and their partners account for over 50% of new infections. We know that incidence is especially concentrated in the EECA and MENA regions, where key populations and their partners account for over 95% of new infections. Furthermore, UNAIDS data also illustrates that the risk of HIV infection is 20 times higher in MSM, PWID, and sex workers—vis-à-vis the general population. Yet in preparation of this document, limited data was available on the risk and burden of AIDS-related mortality borne by key populations<sup>18</sup> and their partners. The data that could be found should—while based on studies in the early 2010s—nevertheless raise serious alarms.

At the very least, the data on these groups certainly shows the extent that key populations have been exposed to AIDS-related mortality in the past. These figures may have since changed. But by how much? And to what degree does such limited coverage in key populations contribute to elevated mortality? The lack of visibility is itself a problem.

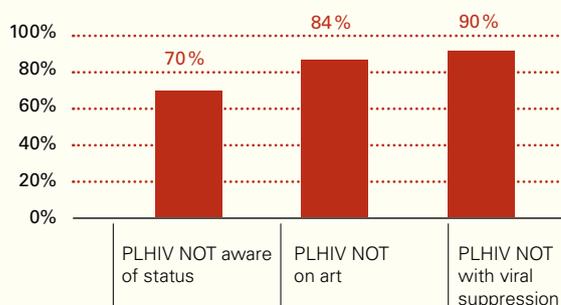
MSM IN MOSCOW (2013)<sup>19</sup>



PWID IN INDIA (2013)<sup>20</sup>



MSM IN INDIA (2013)<sup>21</sup>



**LOTS OF QUESTIONS:  
NOT ENOUGH DATA TO ANSWER THEM**

The absence of robust data on key populations is so worrying precisely because it leaves policymakers blind to the state and dynamic of the epidemic on the ground. West and Central Africa provide a case study in the limited visibility of data on key populations. The UNAIDS Key Population Atlas aims to measure a wide range of indicators related to key populations' access to services. However, for ART coverage, data is largely absent for West and Central Africa across key population categories—sex workers (available for 3 countries), MSM (available for 4 countries), PWID (available for 1 country), transgender (available for 0 countries), prisoners (available for 2 countries)<sup>22</sup>. Without such data, it is not simply impossible to identify risks of further exacerbation of the epidemic tomorrow, it is all the more difficult to address them today.

This document makes the case that we need a better profile of strategic information on AHD and mortality. In laymen's terms, we need better data on:

**Who is dying?**

What are mortality rates in key populations?

**From what diseases?**

What is the local distribution of AIDS-related mortality across OIs?

**Via what pathways to AHD?**

What is the distribution of AHD patients across the spectrum of never diagnosed, late diagnosis, loss to referral, treatment interruption, treatment failure, immune reconstitution failure?

**When?**

When are deaths occurring in relation to engagement with HIV services, treatment initiation, and loss to follow up?

**Where?**

What is mortality by district/region and facility catchment areas?

These questions are important because they are essential to understanding more fundamental questions:

**Why are so many dying?**

**And how can we reduce that mortality?**

# V.

## **MORTALITY IN THE CONTEXT OF THE HIV CONTINUUM FRAMEWORK**

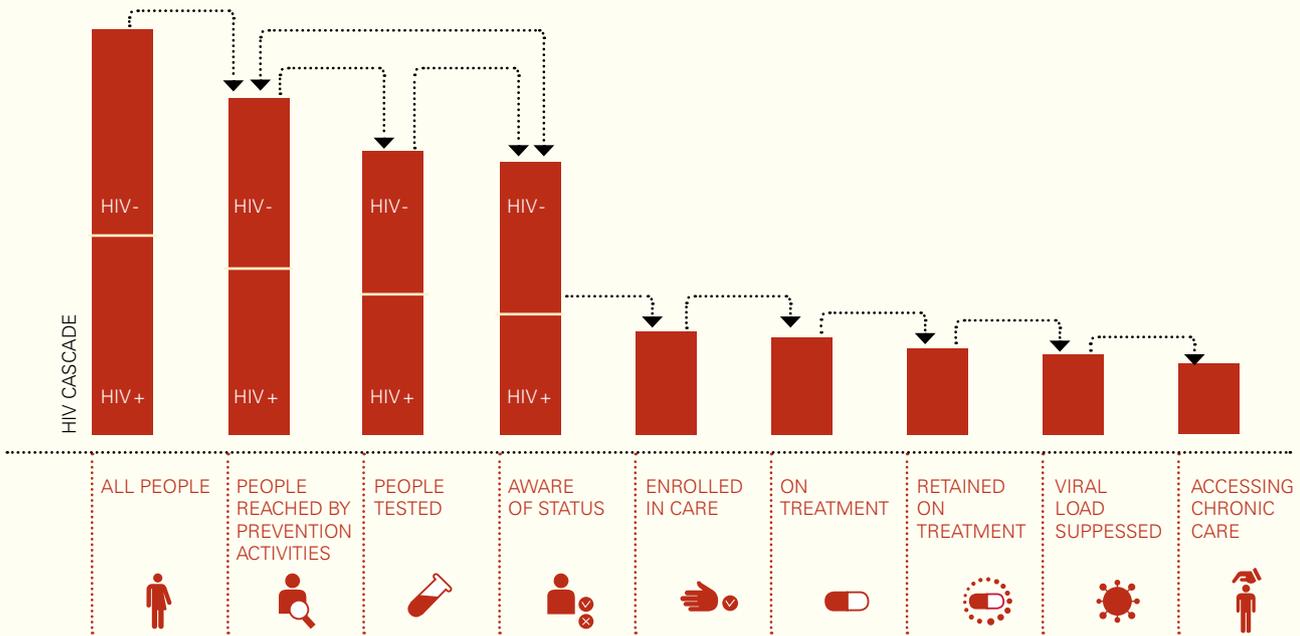
### **REINFORCEMENT OF HIV CONTINUUM PILLARS AS CATALYST TO REDUCING MORTALITY**

The WHO 2016-2021 Global Health Sector Strategy on HIV presents the following HIV<sup>23</sup> Continuum to evaluate the scope of services essential to the HIV response. The HIV Continuum aligns closely with the logic of the 90-90-90 approach, though it builds on that logic by expanding the scope to include broader prevention dynamics. As with 90-90-90, the reinforcement of the HIV Continuum is essential to the success of the HIV response in limiting incidence and limiting mortality. The smaller the gaps between the pillars, the smaller the traffic on the pathways to advanced HIV disease.

### **COMMUNITIES' KEY ROLE IN STRENGTHENING CONTINUUM**

Every year, the HIV response generates more knowledge of the impact of HIV interventions and the factors catalyzing/limiting their scale up. In turn, the weight of evidence increasingly converges on the key role of the community-based organizations in strengthening the performance of the continuum. How? In addition to the increasing precedent for community-led delivery of key interventions, there is long-standing recognition of the ability for community-based organizations to reach those most at risk and bring healthcare to the marginalized. Communities' key role in the success of the HIV Continuum also means they are an essential catalyst in strategies to reduce advanced HIV disease. The figure on next page places these important contributions in the context of the HIV Continuum framework.

# WHO'S HIV CONTINUUM OF CARE FRAMEWORK



## HIGH MORTALITY OF PLHIV WITH AHD IN THE 90-DAY PERIOD AFTER TREATMENT INITIATION

For individuals with advanced HIV disease, study after study has demonstrated that the risk of mortality is highest in the 90 days following ART initiation<sup>24</sup>. In other words, for those with advanced HIV disease, ART alone may not be enough to prevent mortality in the short term. These studies also indicate that the mortality risk is highest in those individuals initiating ART with lower CD4 counts. The elevated risk of mortality contributes to the WHO's strong recommendation that "intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease." Intensified adherence support may involve building awareness of the elevated mortality risk of AHD, supporting adherence to an elevated pill burden, and/or support of linkage to care for opportunistic infections. The support of linkage to care can be particularly important as AHD may also lead to physical impairments that impede timely visits to health facilities. With sufficient capacity-building on advanced HIV disease, community organizations may play a key role in reinforcing the awareness and outreach needed to minimize mortality risk in PLHIV with advanced HIV disease who are initiating ART.

## THE MISSING PILLARS OF THE HIV CONTINUUM

One theme is noticeably missing from the WHO HIV Continuum: advanced HIV disease. The absence of pillars representing the AHD cohort and access to AHD services from the HIV Continuum is fitting in only one sense: its absence captures the lack of emphasis that the HIV response has placed on this key area of intervention.

Opportunistic infections are not only exploiting weakened immune systems, they are also exploiting the currently incomplete strategy. Existing medicine can drastically reduce the risk of death from opportunistic infections. Not only are these interventions effective, they are broadly affordable. Yet today, the coverage of access to a WHO-recommended package of care is minimal.

# VI.

## WHO'S RECOMMENDATIONS FOR ADVANCED HIV DISEASE

### COMPONENTS OF WHO-RECOMMENDED PACKAGE OF CARE INTERVENTIONS FOR ADVANCED HIV DISEASE

The following schema synthesizes the key intervention tools and WHO-recommendations from four guidelines: 2017 guidelines on advanced HIV disease, 2018 guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2018 guidelines on cryptococcal meningitis, and 2019 guidelines on the diagnosis of active tuberculosis in people living with HIV.

AREAS FOR THE PACKAGE	INTERVENTION	CD4 CELL COUNT	ADULTS AND ADOLESCENTS	CHILDREN
SCREENING AND DIAGNOSIS <sup>25</sup>	Sputum Xpert MTB/RIP as first test for TB diagnosis in symptomatic patients	Any	Yes	Yes
	Urine LF-LAM for TB diagnosis in patients with symptoms and signs of TB	Any PLHIV with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill irrespective of signs and symptoms of TB if a CD4 cell count of less than 200 (inpatient) or CD4 less than 100 (outpatient)	Yes	Yes*
	Cryptococcal antigen (CrAg) screening	< 200 cells/mm <sup>3</sup>	Yes	No
PROPHYLAXIS AND PRE-EMPTIVE TREATMENT <sup>26</sup>	Co-trimoxazole prophylaxis <sup>A</sup>	350 cells/mm <sup>3</sup> or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections	Yes	Yes**
	TB preventive treatment <sup>A</sup>	Any	Yes	Yes <sup>#</sup>
	Fluconazole pre-emptive therapy for CrAg-positive without evidence of meningitis	< 200 cells/mm <sup>3</sup>	Yes	Not applicable (screening not advised)
	Rapid ART initiation	Any	Yes	Yes
TREATMENT <sup>27</sup>	Cryptococcal Meningitis	Preferred <sup>o</sup> : short-course (one-week) with amphotericin B deoxycholate and flucytosine Alternative <sup>***</sup> : Two weeks of fluconazole + flucytosine	Yes	Yes
	Drug-susceptible Pulmonary TB	2HRZE/4HR	Yes	Yes
	Drug-Resistant Pulmonary TB	See WHO's consolidated 2019 guidelines	Yes	Yes
ART INITIATION <sup>28</sup>	Defer ART initiation if clinical signs and symptoms suggestive of TB or cryptococcal meningitis <sup>•</sup>	Any	Yes	Yes
ADAPTED ADHERENCE SUPPORT <sup>29</sup>	Tailored counseling to ensure optimal adherence to advanced disease care package, including home visits if feasible	< 200 cells/mm <sup>3</sup>	Yes	Yes

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● WHY IS CD4 PART OF THE PACKAGE OF CARE?

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- \* Limited data available for children.
- ^ Co-trimoxazole, isoniazid and pyridoxine are available as a fixed-dose combination tablet.
- \*\* Priority should be given to all children less than 5 years old regardless of CD4 cell count or clinical stage, and those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4 event and/or those with CD4  $\leq$  350 cells/mm<sup>3</sup>)
- # For children < 12 months of age, only those with a history of TB contact should receive TB preventive treatment. For all receiving TB preventive therapy, active disease should first be ruled out.
  - Consolidation and Maintenance phases recommended after first Induction phase of treatment.
- \*\*\* Another alternative: two weeks of amphotericin B deoxycholate + fluconazole
- TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of treatment (strong recommendation, high-quality evidence); TB patients living with HIV who have severe immunosuppression (such as CD4 cell counts <50 cells/mm<sup>3</sup>) should receive ART with the first two weeks of initiating TB treatment. Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment.

Following the introduction of test-and-treat guidelines, CD4 is no longer a strict gatekeeper to ART initiation. However, the WHO continues to recommend<sup>30</sup> CD4 testing for those first diagnosed with HIV and those re-initiating treatment after a period of interruption. Why? Because during the process of post-ART immune reconstitution (i.e. as the immune system is regaining strength), underlying opportunistic infections may continue to pose serious mortality risks. These underlying infections may be asymptomatic and early detection - before they progress to more dangerous stages - would allow for more effective preventive or pre-emptive interventions. CD4 testing is therefore key to a public health approach to identifying if a patient has advanced HIV disease and ultimately needs to be tested and treated for underlying opportunistic infections. In short, while not the gatekeeper to ART initiation, CD4 testing does serve as a gatekeeper for testing to identify need for key prophylactic and pre-emptive interventions in the package of care for advanced HIV disease.

## BARRIERS TO UPTAKE OF THE AHD PACKAGE OF CARE

We have medicines, we have evidence of their efficacy in preventing and treating opportunistic infections, and we have WHO recommendations. So what is the issue?

- Lack of domestic and international investment to address advanced HIV disease
- National guidelines and local treatment protocols on advanced HIV disease remain out of line with WHO recommendations.
- CD4 testing has been phased out of many national guidelines, and support from donors for CD4 cell count testing has decreased in recent years.
- Screening and diagnostic tests for opportunistic

infections are not adequately funded and remain inaccessible even in countries that have begun to incorporate WHO guidelines.

- Treatment for opportunistic infections remains too expensive or completely unavailable in areas of high need.
- Several essential medicines (e.g. flucystosine) for advanced diseases are not even registered in a wide range of sub-Saharan African countries.
- In part due to the historically limited availability of several commodities in the package of care, health professional in many settings have insufficient awareness of the advanced HIV disease package of care and/or insufficient training on its delivery.

# VII.

## EXAMINING COMMON MISCONCEPTIONS

### 1) 90-90-90 ALONE WILL ELIMINATE MORTALITY

The achievement of 90-90-90 will have an important impact on reducing AIDS-related deaths. Yet even if 90-90-90 is achieved, a significant number of PLHIV will remain at risk of progressing to advanced HIV disease. Without access to a package of care for advanced HIV disease, the risk of mortality for these individuals increases substantially.

### 2) DOLUTEGRAVIR WILL SOLVE EVERYTHING

Access to the integrase inhibitor dolutegravir should provide an important boost to efforts to reduce the development of ART resistance and to offer those resistant to certain antiretroviral medicines an important 2nd- or 3rd-line treatment option. In short, dolutegravir should boost the 3rd 90 (i.e. the percentage of PLHIV on ARV who achieve viral suppression). However, dolutegravir's impact will not extend to those who have not been diagnosed or those who are not on treatment.

### 3) INNOVATIVE TECHNOLOGY WILL SOLVE EVERYTHING

PLHIV who confront barriers to formal engagement in the health system will face obstacles to the uptake of new technology. These barriers may stem from issues related to stigma, lack of awareness, and structural marginalization of PLHIV. Moreover, though technology may alleviate the burden on a given health system and allow for some degree of decentralization and/or simplification of service delivery, new technology alone will not eliminate health system barriers such as insufficient health workforce capacity or health financing.

### 4) ADVANCED HIV DISEASE ONLY OCCURS IN TREATMENT-NAÏVE PLHIV

The percentage of AHD cases that are treatment naïve (i.e. never initiated ART) will vary according to cohorts. In some settings, there is robust data suggesting that treatment-experienced individuals constitute a significant share of PLHIV living with AHD. Treatment discontinuation, treatment interruption, treatment failure, and immune reconstitution failure may all contribute to AHD in treatment-experienced individuals.

### 5) ART ALONE IS ENOUGH

ART is the best means to prevent AHD and initiation of ART is key to immune reconstitution for those experiencing AHD. Yet PLHIV re-initiating ART at the AHD stage will remain at risk of opportunistic infection until OIs are cleared and/or sufficient immune reconstitution has occurred. Reinforcing the fact that ART alone is not sufficient, the WHO 2019 TB Report<sup>31</sup> highlights that 86% of the 477K reported TB cases (in 2018) involved individuals on ART. It should be noted that an estimated 45% of the 860,000 new cases of TB in PLHIV in 2018 were not reported. Moreover, the Temprano study has shown that a combination of early scale up of ARV and TB preventive therapy dramatically lowered mortality rates after 30 months.<sup>32</sup>

**6) CD4 IS NO LONGER RELEVANT**  
.....

The WHO continues to recommend<sup>33</sup> CD4 testing for those first diagnosed with HIV and those re-initiating treatment after a period of interruption. Why? Because CD4 testing is crucial to the process of identifying vulnerability to opportunistic infections that can pose significant mortality risks to PLHIV with advanced HIV disease.

**7) OPPORTUNISTIC INFECTIONS CANNOT BE EFFECTIVELY TREATED**  
.....

Existing tools for the most common OIs have a major impact on mortality from these diseases. One example is cryptococcal meningitis. A disease that is estimated to have a 70% mortality rate when treated with fluconazole alone<sup>34</sup> (currently the most common treatment in many resource-limited settings), the ACTA study recently demonstrated that mortality rates can be reduced to as low as 24% at 10 weeks with the WHO-recommended treatment of flucytosine and amphotericin B<sup>35</sup>.

**8) AIDS-RELATED MORTALITY IS LIMITED TO ADULTS**  
.....

Since 2010, annual mortality in children (0-14 years old) has been reduced from 200,000 to 100,000<sup>36</sup>. Despite this 50% reduction, children living with HIV continue to represent an extremely vulnerable population. Why? Without ART, one in three children living with HIV die in their first year of life, half by the age of two, and four out of every five children die by five years of age<sup>37</sup>. Despite this risk, it is estimated that only 54% of children under 5 years old are on ART. For West and Central Africa, the estimated coverage of ART in children under 5 years old was 28% in 2017<sup>38</sup>.

# VII.

## A CALL TO ACTIONS

At AIDS 2018, several dozen activists intervened during a session attended by high-level representatives of PEPFAR, Global Fund, and UNAIDS. The purpose of the intervention was to call attention to the issue of AIDS-related mortality and to highlight specific mortality-related gaps in the current HIV response. The demands were reiterated in a letter sent in October 2018 to UNAIDS, Global Fund and PEPFAR. That letter, signed by over 50 civil society organizations working on HIV, called for many of the actions highlighted here.

### WE CALL ON:



#### UNAIDS AND WHO TO:

- Develop a concrete global plan aimed at the achieve of the mortality targets; this plan should build on the strategy to expand ART test-and-treat by supporting rollout of testing and treatment to address the leading opportunistic infections as outlined in the WHO recommendations for a package of care for advanced HIV disease.



#### PEPFAR AND GLOBAL FUND TO:

- Provide clear support for the provision of the WHO-recommended advanced HIV disease package of care; this includes procurement of the AHD package of care commodities, as well as support of training of the healthcare workforce for its implementation. Clear instruction on the use of CD4 at ART initiation and re-initiation is absolutely essential. Elaborate—in collaboration with WHO and UNAIDS—a credible plan for healthcare facilities to monitor and report AHD and AIDS deaths in a manner enabling strategic information to assure adapted responses and greater accountability.



#### NATIONAL GOVERNMENTS TO:

- Strengthen domestic financing of the HIV response
- Engage at policy level to facilitate uptake of AHD package of care, including the fast-tracking of registration of AHD commodities and their inclusion in the Essential Medicines List
- Collaborate with UNAIDS and WHO on adaptation of the global mortality reduction plan to the country level

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# ANNEX: RESOURCES

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## FOR FURTHER EXPLORATION

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## OF ADVANCED HIV DISEASE

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*Left behind by the HIV response: Advanced HIV in DRC*  
(MSF Report, December 2017)

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