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WAITING ISN'T AN OPTION: PREVENTING AND SURVIVING ADVANCED HIV



AIDS IN THE TEST & START ERA

In 2015 alone, **1.1 million individuals still died due to HIVⁱ**, despite being in an age of free anti-retroviral treatment (ART) that is more available and effective than ever before. In MSF-supported hospitals in Guinea, DRC, Kenya and Malawi, we witness a **30-40% mortality rate among patients with HIV**. The majority of these patients are hospitalized with CD4 levels less than <200 cells/ μ L, the threshold used to define Advanced HIVⁱⁱ.

CD4 monitoring – at initiation and when people living with HIV (PLHIV) become severely ill – therefore remains critical: it is the best predictor of mortality for PLHIV and allows to quickly identify advanced disease as well as guide clinical management.

The same opportunistic infections (OIs: tuberculosis, cryptococcal meningitis, toxoplasmosis) are consistently associated with advanced HIV, yet there is a lack of access to OI treatment and diagnosis tools like **TB LAM and CrAg**.

In our hospitals, advanced HIV today is not what it used to be: most of our **patients are now ART-experienced**. It further complicates management of those patients because of the balancing act between urgently reconstituting the patient's immune system, while having to manage the risk of viral resistance. **In the community, the majority of people living with advanced HIV are untested and treated**, highlighting the need for innovative HIV testing strategies beyond the clinics.

But **surviving advanced HIV is possible**: it requires quick actions and investments at the community, Primary Health Care (PHC), hospital level and back to the community.

Community

- Reduce barriers to testing (stigma, knowledge, cost) and adherence (treatment literacy)
- Differentiated Models of Care

Primary Health Care

- Routine Viral Load (VL) testing (at least annually)
- Continued CD4 availability at initiation of ART and in ill patients
- Faster switches to 2nd line for failing/advanced patients
- Better drug regimens for HIV
- Free access to OI treatment

Hospital

- Adoption of WHO guidelines on Advanced HIV (2017)
- Access to Point of Care (PoC): TB Lam, CrAg, CD4, VL

And Back to the Community

- Built-in follow up of hospitalized patients after discharge
- A realization that 90-90-90 is not a linear process

ⁱ. UNAIDS, 2015, <http://www.unaids.org/en/resources/fact-sheet>

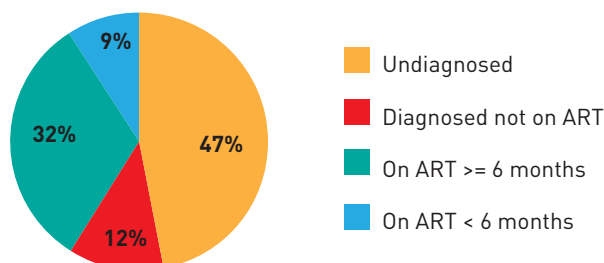
ⁱⁱ. Advanced HIV is defined as a CD4 count of less than 200 cells/ μ L or a WHO Stage III or IV infection.

AVOIDABLE ILLNESS AND DEATH: THE NEED FOR CONTINUED CD4 TESTING

Studies show that **a person's CD4 count at initiation is the most important predictor of mortality**. While some countries have started to abandon CD4 testing, access to CD4, both at initiation and during the person's lifetime on ART remains essential. It helps identify advanced HIV persons early, before they become sick; it can therefore influence their clinical follow-up at the Primary Health Care (PHC) level.

If immunosuppression sets in, it can lead to dangerous OIs: in places where drugs and health services are inconsistently available, the effect can be deadly. Among MSF advanced HIV inpatients in Kenya, of those admitted with TB, 36% died after being admitted. In Kinshasa, 56% of all HIV patients who died after being admitted had TB (case fatality rate [CFR] 35%), another 7% had Cryptococcal Meningitis (CCM) (CFR 38.7%), 12% had toxoplasmosis (CFR 38.7%) and 8.9% had Pneumocystic Pneumonia (PCP) (CFR

Total n = 385 or 9.4% of total



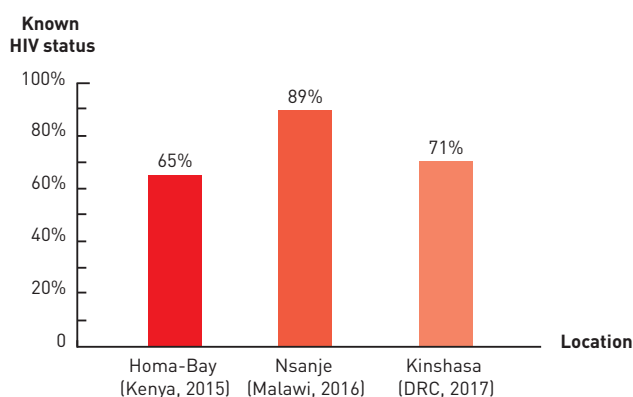
N = 4113 HIV (+)
ART coverage: 74.0%
Total < 200 CD4: n=385

GRAPH 1: ART Status of PLHIV with CD4<200
Epicentre/MSF HIV population surveys Kenya, Malawi & South Africa 2012-2013

48,2%). In Guinea, Conakry, the main causes of deaths include TB and CCM, and delay in diagnosis kills. TB contributes two-thirds of HIV related deaths, and late presentation is a contributing factorⁱⁱⁱ.

THEN AND NOW: ART-NAÏVE VS. ART-EXPERIENCED

A decade ago, advanced HIV was seen mostly among patients who were unaware of their HIV status, often because of a lack of HIV testing and ART availability. Today, however, **in some MSF inpatient facilities, 75% of hospital admissions are for advanced HIV patients who are receiving ARVs**, often for many years (see graph 2). This suggests that they may have, either inherited a resistant form of the virus or that we have failed to identify the dangerous clinical, immunological, or virological signs that a patient's treatment had been failing them for some time.



Graph 2: HIV Status at admission

ⁱⁱⁱ. Ndayisenga et al. *Mycobacterium Tuberculosis Lateral Flow Urine Lipoarabinomannan Assay (TB-LAM) and Cryptococcal Antigen Lateral Flow Assay (CRAG LFA) as Screening among Patients with Advanced HIV-Disease in Conakry, Guinea. 20172017*

ADVANCED HIV: A PATIENT'S JOURNEY



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HIV disease management can be compared to pushing a boulder up an endless mountain, with many stumbles along the way. Viral suppression and health lies at the top, but the boulder may tumble down many times, to various places, even after reaching the summit - perhaps by not adhering to their medications and developing an OI at one point, or by moving to a new location only to re-test and re-initiate treatment at a new health facility. Most patients interact with multiple types of care on their journey, and how heavy or difficult the boulder they are pushing often comes down to factors like the functionality of the health system, access to care and medication, and socio-cultural factors like stigma and community support. HIV actors must accept that HIV care, and the HIV patient's journey to health, is not always a linear process of testing, initiating treatment, consistent drug adherence

followed by a lifelong viral suppression. Rather, **studies have shown that nearly 25% of patients will interrupt their treatment at some point, for some reason, and that these interruptions usually last from a few days to a few months.**^{iv} As a result, community and primary health care and patient support must also be reinforced to enroll (or re-enroll) and retain more PLHIV in care, to prevent their deterioration, unnecessary hospitalization, and death.

Reducing deaths from advanced HIV starts with preventing as many patients as possible from reaching advanced stages. This means combining well-known, context-adapted best practices with new technologies and medications in order to keep people from falling backwards in their treatment journey. It requires renewed efforts at every level of care, along with free access to care.

^{iv}. 2017 WHO Consolidated Guidelines on ARVs (forthcoming)

COMMUNITY LEVEL

MSF continues to see social barriers to health (such as stigma, religious misinformation about the disease, fear, and economic factors, among others) in sub-Saharan Africa. Differentiated Models of Care, such as the Six-Month-Appointment (SMA) or Adherence clubs, along with better psycho-social and community support can prove helpful in removing barriers to retention in care and adherence to treatment. Innovative strategies, such as self-testing and peer-led approaches, are necessary to improve access to HIV testing and linkage to care.

In Malawi for example, studies^v focusing on teenagers- one of the groups facing the most issues with adherence and low levels of CD4 - revealed that social relationships are a major determinant of health. “Adolescents and caretakers have good knowledge on HIV transmission and importance of consistent adherence for their health (...), but lack the skills, practical strategies, confidence and social support to act on this information.” Models of care need to be adapted to the realities facing people living with HIV (PLHIV), and the community they are part of needs to see them as such, offering support, not shame.

PRIMARY HEALTH CARE LEVEL

Preventing HIV patients from reaching advanced stages also demands that primary health care providers serve as a **first line of defense**. Patient management can be strengthened through faster, point of care, diagnosis tools including CD4 testing (see box, page 8), free treatment of HIV and OIs, and better monitoring of treatment failures using viral load (VL) testing routinely.

Of particular importance is **minimum annual viral load monitoring** with quick return of results (i.e. no more than 2 weeks). The absence of results delays measures to rectify the course of the patient's adherence, such as adherence counseling, as well as switching to the next line of treatment.

Delaying switching to the next line of treatment can prove fatal to some. In Chiradzulu, Malawi, MSF found that 80% of the cohort with high first viral load had developed genetic resistance to 1st line treatment and needed to be switched to 2nd line medication^{vi}. Yet in an MSF cohort in Uganda, for example,

only 7.7% of patients with confirmed virological treatment failure were switched within one year.^{vii}

We have to **save lives, not lines**.

Better, affordable, first line treatment for HIV - with fewer side-effects and higher genetic barrier to resistance - would also go a long way in helping to prevent advanced HIV.

Since OIs represent the leading causes of death for advanced HIV patients, finding innovative ways to prevent and treat them is key in reducing mortality linked to advanced HIV. Some examples include Lesotho, where screening for Cryptococcal Antigen (CrAg) was initiated to identify CCM, with concomitant outpatient fluconazole for asymptomatic patients and hospital referral for those with symptoms. This led to an understanding about the need to integrate any roll out of CrAg screening with a better package of screening and care for TB, because this is the major driver of mortality.

^v. Epicentre qualitative study, Chiradzulu, 2017.

^{vi}. MSF-Epicentre 2016

^{vii}. Nicholas et al. *Viral Load Monitoring with Samba-1, a Semi-Quantitative Nearly Point-of-Care Method in Arua, a Rural District, Uganda. 2017*

In Kwazulu Natal, a package of care for PLHIV with CD4<200, to be delivered by nurses and counselors at the clinic level is being developed. It could include blanket TB screening by multiple modalities for all with CD4<200, including TB LAM screening

tests, high dose rifampicin for TB-positive individuals, as well as CrAg screening, fluconazole for positive asymptomatic patients, and enhanced follow up in the community.

HOSPITAL CARE

“Waiting is not an option - the default should be that we do something. We check for TB automatically, for CD4 under 200. The first 6 hours are critical - as people arrive in such a late stage. People just cannot wait 3 days for a CD4 result.”

Dr Rosie Burton, May 10, 2017, Kinshasa

At the secondary health care level, hospitals must treat advanced HIV patients with the speed and urgency of a trauma case: by immediately and correctly diagnosing those

who are advanced (CD4 counts <200 cells/ μ L) and opportunistic infections. Rapid reaction for these patients, by switching drug regimens as quickly as possible, especially when resistance is suspected, is also needed.

Additionally, MSF has worked closely with the WHO to develop the Advanced HIV chapter in the 2017 Consolidated ARV Guidelines, including many of the above recommendations. It is imperative that these guidelines be quickly adopted by national Ministries of Health, and that resources be allocated to implement them at the clinical level to keep more patients from advancing in their disease.

AND BACK AGAIN...

A subset of patients, called “late presenters” is comprised of individuals who have never been diagnosed as well as those who have

their diagnosis but have either never started ART or just initiated their treatment. Population surveys show that undiagnosed

“Three months after my stay in the hospital I was truly better. My CD4 was 93. I came to realize that for me, stigmatization occurs when you say just any old thing to someone who is infected. When I think back to the time I was in the hospital, I get goose bumps. It forces me to take my medications as I should and this is why I wanted to speak out, to try and convince those who are really sick that if they take their medication, like I did, they will live, like me. We can put an end to the stigmatization by sending clear messages regarding HIV. Since December, I have been working in a PODI [Community ART Distribution Point]. I am a community distributor in a pharmacy. I give out the ARVs. My behaviour has really changed, and I have learned a lot, a real life lesson. Today, I am in a relationship. My wife is 5 months pregnant. I thank my God for having had the grace to place Mama Julie in my way.”

Jean-Pierre, born in 1981, was hospitalized in 2010 at the Kabinda Hospital (CHK) with a CD4 of 3. Today, his viral load is undetectable.

DIAGNOSTICS: IDENTIFYING INFECTION TO PREVENT ADVANCED HIV

Tuberculosis (TB) and cryptococcal meningitis (CCM) remain HIV patients' primary co-morbidities and are also the primary causes of hospitalization and mortality. In many MSF HIV projects, advanced HIV patients are being systematically screened for these infections using PoC technologies that conduct tests on site and return results quickly. During the first 6 months of systematic screening in an MSF clinic in Conakry, Guinea, 32% of those tested were diagnosed with TB and 4% with CCM.

These technologies are making it easier to quickly start them on treatment. Access to these tools can therefore help save the lives of people living with advanced disease.

The **TB-LAM Rapid Test** (so called because of its detection of the LAM antigen present in TB-infected person's urine) is a PoC technology that can give results in 25 minutes and does not

demand a sputum sample.

TB LAM was used and studied by MSF in Malawi and Mozambique in 2016 for extremely immunosuppressed hospital patients (those with CD4 <200 and <100 cells/ μ , respectively). Using this tool returned TB test results 2-7 times faster than traditional laboratory tests, and enabled TB-infected patients to initiate treatment the same day. Nearly all patients given the TB LAM test received a result, compared to only two-thirds of patients who received results using traditional sputum testing, or less than half who received results using chest x-rays.

Similarly, **Cryptococcal Antigen (CrAg)** testing is making diagnosis of cryptococcosis simpler, faster, more reliable, and more cost-effective. It also allows the identification of patients with early cryptococcal infection who qualify for preventive treatment as outpatients.

and untreated individuals represent 56% of HIV-infected people with advanced HIV in the wider community, yet only 25% of the HIV-infected people being admitted to hospital are untested and untreated. This suggests that a significant proportion of the "late presenters" group is dying in the community without ever reaching the hospital. A qualitative MSF study in rural Malawi and Kenya also found

that after experiencing a life-threatening illness prior to switching regimens, patients felt more dedicated to adhering to a 2nd or 3rd line regimen, feeling they had been given a "second-chance at life." ^{viii} But without support of their community and follow-up from the health system, the weight of HIV will be quickly felt again.

CONCLUSION

In the era of test & treat, people living with advanced HIV are teaching us important lessons. The 90-90-90 policy has proved a noble objective for the HIV community worldwide. However, it fails to acknowledge the importance of treatment failure and the persistence of advanced HIV. Patients do not simply progress through the 3 stages in a linear fashion: they move through various steps throughout their lives. Which is why HIV

patient follow-up – both in terms of loss to follow-up at the primary healthcare level, as well as after leaving the hospital – is key to the survival of those living with advanced HIV. Indeed, in Homa Bay, post-discharge mortality rate was 22% within 35 days. The person living with HIV can never be rid of their charge – their boulder – but better understanding advanced HIV patients' realities can help make the road a lot less steep.

^{viii}. Burns et al. "Because my Life is More Important": Findings from a Qualitative Study on Adherence to Second and Third-Line Antiretroviral Therapy Regimens in Rural Malawi and Kenya. 2017

HOMA BAY, KENYA: FAILING TREATMENT AND DYING UNNECESSARILY

In Kenya, as in much of Sub Saharan Africa, the HIV epidemic remains a leading cause of illness and death, and is a significant burden on an already strained healthcare system that suffers from shortages of medical care providers and urban-rural and regional imbalances. Homa-Bay County (HBC) has the highest adult HIV prevalence in Kenya (25%), one of the highest rates in the world, even though its hospital became the first public medical facility in the country to introduce free ART in 2011.

Gaps in the System

In the MSF-supported hospital of Homa Bay, nearly half of all patients are HIV+, 65% of who have already been on ART. This indicates an inability of the primary healthcare system to identify treatment failure earlier, allowing PLHIV to deteriorate considerably. Despite high HIV prevalence and ART coverage, the county still suffers from limited access to viral load testing technology and has high rates of dropout among HIV patients receiving treatment. Over half (51%) of PLHIV were shown to be taking an ART regimen that is failing to treat their disease, yet switching patients from 1st to 2nd line treatment remains challenging. Specific guidelines allowing a more rapid switch from failed 1st line ART to 2nd line regimens may decrease mortality for people living with advanced HIV. Their drug resistance patterns could also be better monitored with viral genotype testing, but this remains largely unavailable in Kenya and most other resource limited settings.

Snapshot: HIV In Kenya

- HIV prevalence rate: 27.1% Homa Bay County, vs 6% nationally
- High ART Coverage: 59% of HIV+ patients on ART
- Average of 1 physician per 26,400 people, and 1 nurse per 2,460
- 49.1% of all hospitalized inpatients in Homa Bay County were HIV infected
- 36,000 HIV related deaths in 2015

**Sources: UNAIDS, MSF, Epicentre*

What does this mean for Advanced HIV patients?

In the end, 74% of HIV+ patients admitted to Homa Bay hospital were in state of clinical treatment failure (WHO Stage III or IV illness) and two-thirds (66.7%) of these patients were also viraemic (viral load > 1,000cp/ml). Unacceptably high levels of HIV+ inpatients are dying in Homa Bay: 42% overall died after being admitted (16.7% while still in the hospital and 30.4% after being discharged) despite being in a high coverage, middle income, stable country. Too many patients at Homa Bay Hospital are admitted with advanced HIV and opportunistic infections, such as TB and CM, for which rapid diagnostic tests and treatments exist. The implementation of standardized guidelines on how to treat Advanced HIV, such as developed by the WHO, could go a long way in ensuring faster treatment of advanced disease and reducing mortality for people living with advanced HIV.

KINSHASA, DEMOCRATIC REPUBLIC OF CONGO: BARRIERS TO CARE AND LACK OF SUPPORT

The Democratic Republic of Congo's (DRC) health system is overwhelmed by a large population, political and bureaucratic dysfunction, and decades of intermittent conflict. Despite a low HIV prevalence, fewer than 20% of all health centers in the populous urban capital, Kinshasa, offer HIV services (including prevention, testing, and free care). Centers that do offer free HIV services are often overcrowded, staff underpaid and unmotivated, and impoverished patients charged numerous "informal" fees as a result. Stockouts of ARV, HIV test kits, and basic antibiotics such as co-trimoxazole are common. In an MSF study of ART warehouse facilities in Kinshasa, when stockouts of HIV drugs occurred, patients were sent home without any medication nearly 40% of the time.

In the MSF hospital in Kinshasa, mortality among advanced HIV patients is high: 22.6% of hospitalized MSF patients died in 2014 (68% of whom were women). A third of these deaths (34%) occurred within 48 hours of admission, and 78% of these patients had already been on ART for some time (a median of six years). Deaths were associated with several factors: having interrupted treatment within the three months prior to hospitalization, with tuberculosis co-infection, or with a CD4 count <100 cells/ μ L at admission, all of which were common.

MSF interviews^{IX} with HIV patients, caregivers, and health staff reveal a tangled web of individual, community, cost, and health-care system related factors that created barriers to lifelong HIV treatment in Kinshasa. At the individual level, stigma and fear of disclosure, lack of knowledge about HIV, and patients' misunderstanding of their own diagnosis and treatment history all were common, as were low rates of HIV diagnosis, disclosure of their HIV status to those around them,

Snapshot: HIV In DRC

- 1.2% HIV prevalence rate, but higher in key populations:
 - 6.9% in Commercial Sex Workers
 - 8.2% in Men Who have Sex with Men
 - 12% in TB patients
- Low ART Coverage : <30% of HIV+ patients on ART
- 70% of HIV+ admitted to MSF hospital with CD4<100 cells/ μ L (MSF)
- 22,000 HIV related deaths in 2015

*Sources: UNAIDS, MSF

adhering to their treatment, or seeking medical assistance when they are ill. Familial and community support was often lacking, and a powerful church influence also impeded care: Reports of local pastors preventing people from accessing or taking ART, promoting 'miracle' healing over medication, were common. Hidden and informal costs for every interaction with health care was also a significant burden.

What does this mean for Advanced HIV patients?

Both structural and societal forces combine in Kinshasa to make living with HIV extremely difficult. Even for those who manage to get diagnosed and start treatment, inconsistent adherence to medication leads to treatment resistance in too many cases, and resulting mortality rates are alarming. Women are disproportionately affected. Addressing these challenges will require closing gaps in access to care and medication, including the elimination of informal fees. Supporting patients with both material support and correct health information is critical.

IX. Venables et al. *Reasons patients delay seeking treatment for advanced HIV in Kinshasa, DRC, 2017*

ADVANCED HIV: A CALL TO ACTION

Regional Differences

The challenges that result in more advanced HIV patients are not unique to a single area, yet there are specific issues that are more pronounced by region. In **West and Central Africa**, where HIV prevalence, testing, and ART coverage are low, many people living with HIV don't know their status and/or cannot access treatment. In this region, fear and stigma prevent many patients from accessing care until they are very sick; insurmountable costs and centralized HIV care all contribute to the high numbers of patients developing advanced HIV.

In **Southern and Eastern Africa**, where both HIV prevalence and ART coverage are high, the above challenges also exist. Yet, for many advanced HIV patients in this region, other factors are at play: a large number are becoming increasingly resistant to ART, whether they inherited a resistant form of the virus, have been on ART for a very long period of time, or may be facing adherence challenges. Viral load monitoring is essential, yet is not widespread or used systematically, delaying detection and action on treatment failures; OI drugs and diagnostics are often insufficient.

Community level

- Establish Models of care that are adapted to the needs of PLHIV, especially for unstable and non-naïve people, and the realities of their communities (adapted points of distribution & frequency of refills).
- Encourage stigma-reduction and treatment

literacy initiatives that reduce barriers to testing and seeking treatment in communities, and promote adherence.

Primary Healthcare Level: identify early failure

- Continued CD4 testing at initiation: best predictor of mortality
- Enhanced counselling and treatment literacy by dedicated and trained staff
- Better drug regimens for HIV: less side-effects and constraints that reduce adherence, and higher genetic barrier to resistance.
- At a minimum, annual & regular VL; CD4 testing when in therapeutic failure
- Faster switches to 2nd line for failing/advanced patients
- Access to CrAg & TB LAM for CD4<100
- Faster, innovative treatments of OIs

Hospital Level: reactive treatment of people with advanced HIV

- Swift adoption by countries of WHO advanced guidelines, with appropriate resources for training and necessary tools to implement.
- Adoption of key diagnostics tools (CD4 at initiation and in hospitals, VL annually, TB Lam, CrAg)

Post-Hospital care & back to the community

- Built-in follow-up of advanced HIV patients
- A realization that 90-90-90 isn't a linear process; patients will cycle through the steps throughout their lives.



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