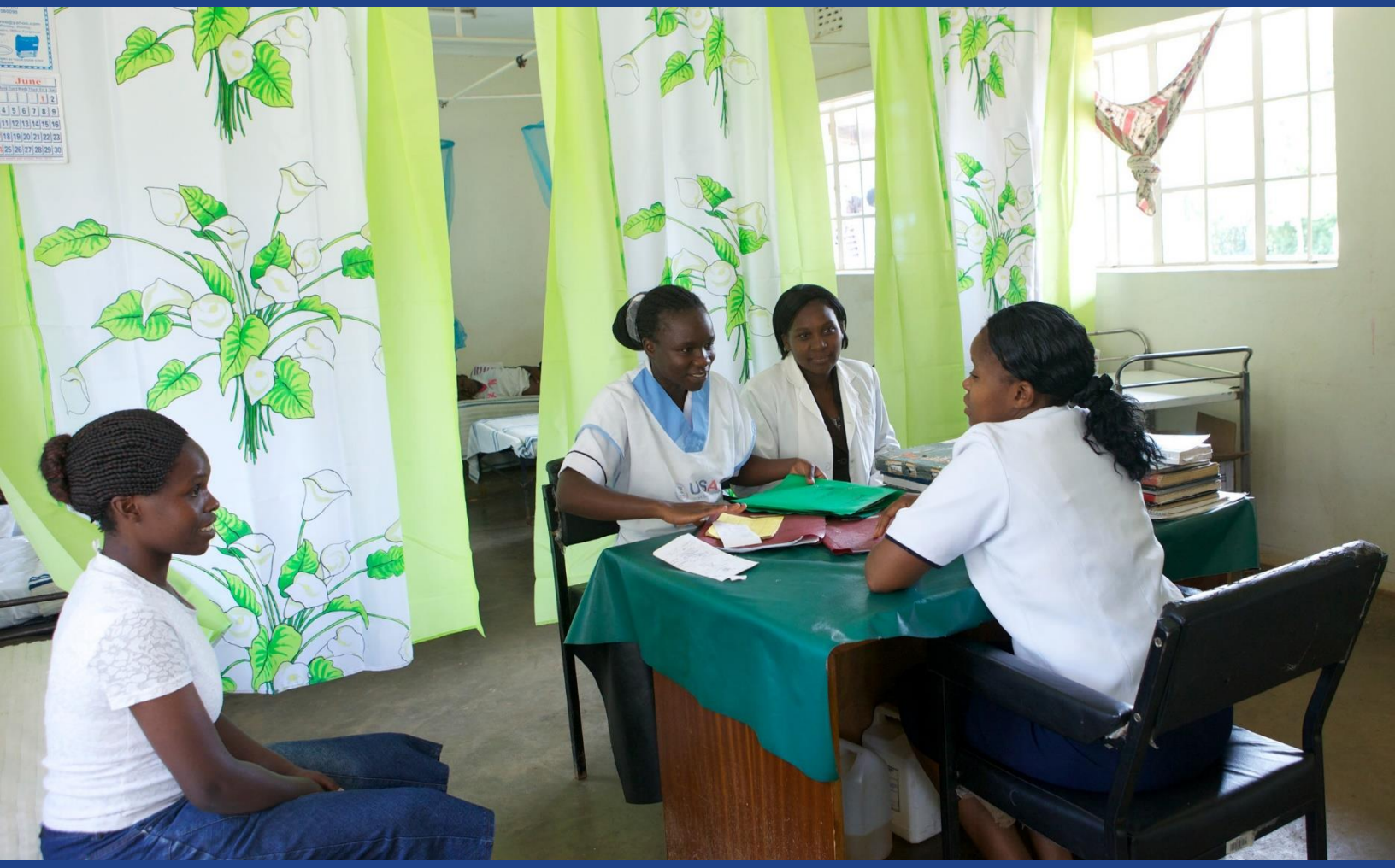
Differentiated Care for Adults at High Risk of HIV Disease Progression



A Call to Action

March 2019

HIV LEARNING NETWORK
The CQUIN Project for Differentiated Service Delivery

ICAP
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Columbia University
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The goal of the HIV Coverage, Quality, and Impact Network (CQUIN) is to increase the number of people living with HIV that initiate and sustain highly effective HIV treatment to achieve long-term viral suppression. Towards this end, ICAP aims to catalyze the delivery of high-quality differentiated service delivery, by enabling experience sharing, joint learning, and collaborative problem solving amongst CQUIN network countries. There is more information about CQUIN at cquin.icap.columbia.edu.

The CQUIN Learning Network is funded by the Bill & Melinda Gates Foundation.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ALUP	Advanced, late, and unstable patients
ART	Antiretroviral therapy
ARV	Antiretroviral
CM	Cryptococcal meningitis
CPT	Cotrimoxazole prophylactic treatment
CrAg	Cryptococcal antigen
DC	Differentiated care
DSD	Differentiated service delivery
EAC	Enhanced adherence
counseling HCW	Health care worker
HF	Health facilities
HIV	Human immunodeficiency virus
ICAP	ICAP at Columbia University
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
MDT	Multidisciplinary team
NCD	Non-communicable disease
NIMART	Nurse-initiated and managed
ART OI	Opportunistic infection
PLHIV	People living with HIV
SIPOC	Severely immunosuppressed package of care
TASO	The AIDS Support Organization
TB	Tuberculosis
VL	Viral load
WHO	World Health Organization

Background/Rationale

The scale-up of antiretroviral therapy (ART) is one of the world's great public health success stories. Nearly 22 million people living with HIV had access to ART in 2017, five-and-a-half-times more than just a decade ago.[1] The annual number of global deaths from AIDS-related illness declined from a peak of 1.9 million in 2004 to 940,000 in 2017.[1] Increased access to prevention and treatment has contributed to a decline in new infections, from a peak of 3.4 million in 1996 to 1.8 million in 2017.[1,2]

Despite these remarkable successes, there are challenges to continuing business as usual when it comes to the design and delivery of HIV programs. Changing clinical guidelines that adopt a 'Test and Treat' approach and the ambitious UNAIDS 90-90-90 global targets have markedly expanded the number of people eligible for ART. In order to meet the UNAIDS 90-90-90 targets, the number of people on ART would need to exceed the reported net increase of 2.3 million people in 2017 and add 2.8 million people each year over the next three years.[1] Unfortunately, global funding for HIV has plateaued, and countries must do more with less when it comes to HIV programming. A second challenge is that the growing number of people on ART has led to overcrowding at health facilities (HF), longer waiting times for recipients of care, and larger workloads for clinicians, all of which compromise the quality of services and patient and provider satisfaction. Finally, gaps in program implementation, such as suboptimal retention rates, threaten both individual outcomes and public health goals.[3]

In response to these challenges, global guidelines now support the use of *differentiated service delivery* (DSD), moving away from a "one-size-fits-all" facility-based model towards different algorithms and programmatic design for diverse groups of people living with HIV, while maintaining public health principles.[4, 5] By varying the design and delivery of services offered to different groups, DSD aims to enhance quality, efficiency, and satisfaction for recipients of care and health care workers (HCW). It puts the recipient of care at the center of service delivery, while ensuring the health system is functioning in a clinically and programmatically-relevant and efficient manner. Key elements of this approach include re-assessing the "when, where, who, and what" of HIV services for groups with different clinical, psychosocial, and contextual characteristics.[6] The World Health Organization (WHO), the President's Emergency Plan for AIDS Relief (PEPFAR), and an increasing number of national ministries of health have endorsed the DSD strategy.

In recent years, the evidence base for DSD for stable patients has grown. Innovative pilot programs have explored approaches, such as facility-based individual models, facility-based group models, community-based individual models, and community-based group models.[7] In contrast, there has been less attention to developing DSD models for individuals with advanced or unstable HIV disease. Clinical guidelines and policies regarding optimal packages of care for high-risk patients exist,[8,9] but most suggest (or imply) the delivery of these services through usual facility-based models. They give few or no recommendations about how, by whom, or where in relation to delivery for optimal impact. One exception is a call to action by Médecins Sans Frontières (MSF) entitled *Waiting isn't an option: preventing and surviving advanced HIV*, which includes recommendations about the "where," including interventions for the community, primary health care facility, and hospital levels.[10]

Thus, although WHO and a number of national HIV treatment guidelines have specific guidance for which interventions and services to provide to patients with advanced or unstable HIV, DSD models addressing the "how" rather than the "what" do not have a wide evidence base, and these elements are rarely specified in guidelines (Appendix A). We reviewed the evidence base on optimal programmatic models for HIV-positive people at high risk to identify best practices and resources for the "how" of differentiated HIV services for these populations. We found very few examples in either the published

or grey literature. This suggests a need for innovative thinking and pilot projects to optimize program design for people with advanced or unstable HIV disease.

Development of differentiated models for people with advanced or unstable HIV disease will be a priority as DSD expands and matures. This document defines the target populations of interest, describes the currently recommended packages of care, and reviews existing DSD models. It will serve as a call to action to motivate stakeholders to share their experiences, generate new evidence, and to advocate for attention to this high-risk population.

Defining High-Risk Patients

People living with HIV on ART that are at high risk of poor clinical outcomes include (1) people with advanced disease who have initiated ART within the past year, and (2) people who have been on ART for a year or more, but are considered "unstable" due to a range of challenges, including unsuppressed viral load (VL), adverse drug reactions, advanced immunosuppression, active opportunistic infections (OI), nonadherence with ART, substance use, mental illness, and other comorbidities requiring close follow-up (Figure 1, Table 1).

Figure 1: Overview of Patient Classification for Differentiated Care (*ICAP Approach to Differentiated Care*, 2017)[11]

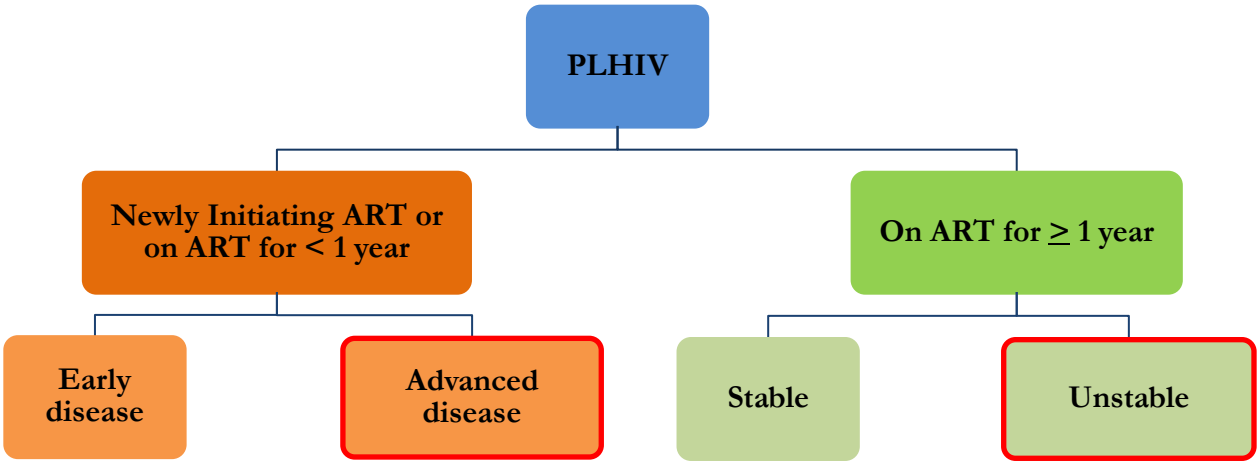


Table 1: Defining High-Risk Recipients of Care

Advanced HIV Disease[9]	Unstable[11]
Adults, adolescents, and children older than the age of five years:	On ART for >1 year and any of the following:
Newly initiating ART or on ART for <1 year	Not virally suppressed*
CD4 <200/mm^3 or	CD4 <200/mm^3
WHO stage III/IV	Adverse drug reaction requiring ongoing monitoring
Children ages younger than five years:	Active OI, including TB
All children ages younger than five years with HIV are considered as having advanced HIV disease	Non-adherent with ART**
	Substance use
	Comorbid condition(s) requiring frequent follow-up
*Not virally suppressed = most recent VL>1,000 and/or no VL in the past six months **Non-adherent = two or more missed doses a month for patients on once-daily regimens, four or more missed doses a month for patients on twice-daily regimens; and/or misses drug pickups	

The *ICAP Approach to Differentiated Care*[11] provides detailed recommendations for the management of patients in each of the four groups identified in Figure 1. This review document builds upon that resource to provide a closer look at the evidence base informing models of care for patients at risk for poor clinical outcomes as defined above. We first describe the package of care for such patients (the "what"), and then summarize our findings on programmatic models (the "how").

The Package of Care: Identifying the "What"

This section describes the recommended packages of care – the "what" for people who are new to ART with advanced disease and for unstable patients on ART, including information from the updated *WHO Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy* in July 2017.

1. Advanced HIV Disease

In 2017, WHO defined advanced HIV disease as follows: for adults, adolescents, and children older than the age of five years, CD4 cell count <200cells/mm^3 or WHO stage 3 or 4 event; and all children younger than the age of five years presenting with HIV.[11] Pooled data from 55 countries in the IeDEA and COHERE regional cohorts show that the proportion of patients starting combination ART with CD4 cell count <200/μL was 55%, ranging from 56% in low-income, 58% in lower-middle-income, 68% in upper-middle-income, and 38% in high-income countries.[12] Although many global and national guidelines recommend starting ART for all people living with HIV, the majority of individuals initiating ART do so with advanced immunosuppression.[12]

HIV-positive adults with CD4 cell counts <200 cells/mm^3 are at significantly higher risk of mortality than those who are less immunosuppressed, and mortality is even more strongly associated with individuals whose CD4 cell counts are <50 cells/mm^3. [13, 14, 15] These recipients of care have a less favorable response to ART compared to those that initiate treatment earlier in the course of HIV infection, and have a less robust CD4 count recovery on treatment.[16, 17] In addition, they are at high risk of OI. For example, the incidence of tuberculosis (TB) in untreated people living with HIV is between 10 and 30 times higher in those with a CD4 count <50 cells/mm^3 compared to those with a CD4 count of ≥500 cells/mm^3.[18] CD4 cell count at the time of ART initiation is one of the strongest predicators of mortality,[19, 20, 21] and mortality within a year of HIV diagnosis is ten times higher for people that present with advanced disease.[22]

The Package of Care

Achieving immune system recovery with ART is the primary means to reduce morbidity and mortality related to HIV disease, and delays in ART initiation result in avoidable suffering and deaths.[23] Strategies to reduce early mortality and morbidity among people living with HIV that present to care with advanced disease include: prompt initiation of OI prophylaxis; screening and treatment for co-morbid conditions; swift initiation of ART for those without active cryptococcal infection; and close follow-up and monitoring to support adherence and diagnose and appropriately manage complications, such as adverse drug reactions and/or immune reconstitution inflammatory syndrome (IRIS).[24]

Table 2 illustrates the package of interventions recommended for people with advanced HIV disease in the 2017 *WHO Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy.*[9] These recommendations are also included in several national HIV treatment guidelines, including those from Kenya, Uganda, Ethiopia, Tanzania, Zimbabwe, and Eswatini. The *ICAP Approach to Differentiated Care* and some national guidelines also specify the need for intensive management of any presenting illnesses, close monitoring for IRIS, and ongoing adherence counseling.

Table 2. WHO Package of Care for Patients with Advanced Disease[11]

Intervention	CD4 cell count	Adults	Adolescents	Children
Diagnosis				
Sputum Xpert® MTB/ RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes
LF-LAM for TB diagnosis among people with symptoms and signs of TB	≤100 cells/mm^3 Or at any CD4 count if seriously ill	Yes	Yes	Yes[a]
Cryptococcal antigen screening	≤100 cells/mm^3	Yes	Yes	No
Prophylaxis and pre-emptive treatment				
Co-trimoxazole prophylaxis[b]	≤350 cells/mm^3 or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial Infections	Yes	Yes	Yes
TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
Fluconazole pre-emptive therapy for CrAG-positive people without evidence of meningitis	<100 cells/mm^3	Yes	Yes	Not applicable (screening not advised)
ART initiation				
Rapid ART initiation	Any	Yes	Yes	Yes
Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis	Any	Yes	Yes	Yes
Adapted adherence support				
Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm^3	Yes	Yes	Yes

[a] Limited data available for children.
[b] Cotrimoxazole, isoniazid, and pyridoxine are available as a fixed-dose combination tablet.
[c] For children ages younger than 12 months, only those with a history of TB contact should receive TB preventive treatment if the evaluation shows no TB disease.

Cotrimoxazole prophylactic treatment

Cumulative evidence from observational data and randomized clinical trials supports the value of cotrimoxazole prophylactic treatment (CPT) in resource-limited settings in reducing hospitalizations, morbidity, and mortality among people living with HIV.[25] Despite an increasing understanding of the potential impact of CPT in resource-limited settings, wide-scale implementation of CPT programs has been slow and suboptimal.[26]

Tuberculosis

Tuberculosis and HIV are intimately related. TB is the most common, serious OI amongst people living with HIV, and the leading cause of death from a single infectious agent, ranking above HIV/AIDS.[27] The WHO strongly recommends that all people living with HIV receive screening for TB symptoms at each clinic encounter, with expedited TB diagnosis and treatment for presumptive TB cases and prompt initiation of isoniazid preventive therapy (IPT) upon the exclusion of active TB.

In recent years, the WHO has endorsed the use of molecular diagnostics such as Xpert MTB/RIF and urine testing for mycobacterial lipoarabinomannan (LAM) for use in symptomatic patients with advanced HIV and signs or symptoms of TB (e.g., hospitalized patients with CD4 cell counts <100 cells/mm$^{3)}$.)[28, 29]

The use of IPT and ART have shown to have additive benefits on reducing TB incidence and mortality compared to IPT or ART alone.[30, 31] Unfortunately, IPT coverage remains low, with fewer than 25% of eligible patients receiving IPT.[32] In 2017, 958,559 people living with HIV were reportedly started on IPT.[27] The *WHO Guidance on the Programmatic Management of Latent TB Infection* issued in 2018, recommends four options for treatment of LTBI, including new, shorter drug regimens: a weekly dose of rifapentine and isoniazid for three months, a daily dose of rifampicin plus isoniazid daily for three months, a daily dose of of rifampicin for three to months or a daily dose of isoniazid for at least six months.[27, 33]

Based on evidence of the efficacy of ART initiation on reducing mortality among patients with HIV-related TB, WHO recommends early initiation of ART in HIV-positive TB patients, specifically within the first eight weeks of TB treatment, and within the first two weeks of initiating TB treatment for HIV-positive TB patients with CD4 counts <50 cells/mm^3.

Cryptococcal meningitis

In sub-Saharan Africa, cryptococcal meningitis (CM) is a leading cause of death among people with advanced HIV, both before and after ART initiation. The risk of CM is highest among severely immunocompromised patients and is most common in those with a CD4 count less than 100 cells/mm^3.[34] Routine serologic screening for cryptococcal antigen (CrAg) in people living with HIV with CD4 cell count less than 100 cells/mm^3, early detection of cryptococcemia, and pre-emptive treatment with fluconazole prior to initiation of ART have shown to decrease overall mortality and the risk of CM-associated IRIS among this population.[35] WHO recommends CrAg screening in ART-naïve adults with advanced disease.[9]

Opportunistic infection prophylaxis

Additional OI prophylaxis interventions were evaluated in the REALITY trial. An enhanced antimicrobial prophylaxis package consisting of five days of azithromycin (500 mg), single-dose albendazole (400 mg), at least 12 weeks of INH/pyridoxine (300/25 mg), and 12 weeks of fluconazole (100 mg), in addition to continuous CPT, was compared to standard CPT prophylaxis. Results published in 2017 demonstrated that, while there was a reduction in mortality among people with CD4 <100 cells/mm^3 receiving an enhanced prophylaxis package at 24 and 48 weeks compared to those receiving CPT alone, these findings were not statistically significant.[36] While national guidelines currently do not recommend the use of enhanced prophylaxis, some programs are piloting the approach. The Lighthouse Trust in Malawi, for example, will include the enhanced prophylaxis package in its Advanced, Late, and Unstable Patients (ALUP) protocol starting in 2017.[37]

Optimal adherence to ART is critical for HIV treatment success, including sustained HIV viral suppression, reduced risk of drug resistance, improved quality of life and survival, and decreased risk of HIV transmission. To avoid treatment failure, adherence preparation, monitoring, and support are strongly recommended as critical components of the package of care for all patients initiating ART.

In many countries, key services include adherence counseling, patient education, support groups, and community-based outreach, although these vary in design, intensity, and availability. Adherence is often challenging during the first few months of treatment, and most guidelines recommend

intensive, multidisciplinary support until patients achieve virologic suppression. Given the urgency to start ART in people presenting with advanced disease, and the recommendation for same-day ART initiation for some individuals, accelerating delivery and developing innovative methods of delivering adherence and psychosocial support concurrently with ART are programmatic priorities (see below).

2. "Unstable" Patients on ART

Although more than 90% of people living with HIV achieve viral suppression within a year of starting ART,[38,39] they do not always achieve or maintain viral suppression. In addition, some people who have been on ART for a year or more may face other challenges that lead to characterizing them as "unstable." As seen in Table 1, this includes people on ART with a CD4+ count <200 cells/mm^3, active OI, adverse drug reactions requiring monitoring, non-adherence with ART, substance use, mental illness, and/or other comorbid condition(s) requiring frequent follow-up and intensive support.

"Unstable" patients on ART are a heterogeneous group, but all are at high risk for poor clinical outcomes, including complications and/or treatment failure. People living with HIV on ART who continue to have evidence of advanced immunosuppression require close monitoring because of their high risk for OIs. Patients with active OI, adverse drug reactions, and/or comorbid condition(s), such as cardiovascular, renal, or hepatic disease, require intensive clinical management to avoid morbidity and mortality due to those conditions, and to ensure adherence to ART during their management. People living with HIV with VL>1,000 copies/ml, adherence challenges, and psychosocial challenges, such as substance use and mental illness, require enhanced adherence support to avoid treatment failure.

People on ART who do not achieve and maintain plasma HIV RNA<1000 copies/ml, or who experience virologic rebound, may develop ART resistance mutations. Managing individuals with ART resistance usually requires consultation with an HIV expert or a multidisciplinary team (MDT). In some programs, a second-line committee reviews patients with suspected first-line failure to approve second-line regimen use.

The Package of Care

The package of care for unstable patients on ART generally falls into several overlapping categories: (a) intensive and/or advanced clinical care for individuals with acute OI, drug reactions, and co-morbid condition(s); (b) enhanced adherence support with frequent virologic and immunologic monitoring for patients with VL>1000 copies/ml and known or suspected nonadherence, and (c) advanced ART management for patients with known or suspected drug resistance. In addition, common elements for unstable patients include the need for more frequent visits (generally every one to two months), service delivery by specialist clinicians (particularly in case of suspected ART resistance), and intensive psychosocial/adherence support.

Adherence assessment should be conducted for all patients with suspected or confirmed treatment failure (e.g., those on ART for at least six months who have a VL>1,000 copies/ml, a decline in CD4+ count, or lack of improvement or worsening clinical condition). Suboptimal adherence is often, but not always, the reason for treatment failure, and an MDT should always conduct a careful, multidisciplinary assessment as indicated. Ideally, a MDT will assess all potential causes of treatment failure including non-adherence, inadequate dosing, drug-drug interactions, drug- food interactions, impaired absorption (e.g., chronic severe diarrhea), and drug resistance, if available.

Adherence assessment should include a supportive discussion with the patient about medication usage, review of medication pick-ups, consideration of pill counts, a home visit, and discussions with treatment supporters, caretakers, and/or spouse/partners, if the patient agrees.

Enhanced adherence counseling (EAC) aims to assess adherence barriers in a nonjudgmental way, and to help the patient construct a personalized adherence plan with concrete objectives. It is important not to focus solely on knowledge of HIV and ART but also to review psychological, emotional, and socio-economic factors that may contribute to poor adherence. In addition, exploring the patient's motivation for taking medication often highlights reasons for poor adherence. Several national guidelines recommend at least three EAC sessions, followed by a repeat VL testing, although no definitive comparison of EAC approaches has been conducted. [40]

Differentiating Services: Identifying the "How"

The previous section briefly reviewed the packages of care recommended for high-risk patients – the what. To understand how these services are delivered, and to identify differentiated models of care for people living with HIV at high risk for poor clinical outcomes, we reviewed the published and grey literature, and reached out to diverse implementers to learn more about the "where, when, and who" of program design for this subgroup of patients. We also reviewed national ART guidelines from eleven countries in sub-Saharan Africa (see Appendix A and B). In order to synthesize the findings, we categorized key challenges and barriers to effective service delivery for high-risk patients (Table 3) and describe innovations and best practices developed to address them. Increasingly, there are emerging innovations and best practices implemented, such as the Severely Immunosuppressed Package of Care (SIPOC) model in Kenya and the MSF advanced HIV package for seriously ill patients described below. Other innovations have been identified in the context of implementation science studies, such as the SEARCH study in Uganda[41] and Link4Health in Swaziland, among others.[42]

Table 3: Key challenges and barriers to service delivery for recipients of care at high risk of disease progression

Challenge	Illustrative Barriers/Challenges
Identification of high-risk recipients of care	Delayed linkage from testing to treatment
	Delayed ART eligibility assessment
	Delayed identification of failing regimens
ART initiation and management	Lack of standard operating protocols for high risk patients
	Delayed switch to second and third-line regimens
Prevention and management of acute co-morbid conditions(s)	Insufficient or absent OI screening/prophylaxis
	Weak linkages for up-referral to more specialized site/providers
	Discontinuity between inpatient, outpatient, and community-based services
	Siloed HIV and NCD services
Management of chronic co-morbid condition(s)	Lack of strong home care systems
	Need for specialized adherence support

1. Timely Identification of High-Risk Patients

As noted above, the majority of people living with HIV initiate ART with advanced immunosuppression, missing a critical opportunity to prevent complications of HIV and to maximize the chance of sustained treatment success. Optimizing HIV testing services to identify HIV-positive people early in the course of HIV infection is an essential element of effective HIV programming, and a wealth of innovative program models continue to be piloted. The use of point-of-care CD4 testing, able to provide same-day results, has enabled programs to rapidly identify patients with advanced disease and accelerate their linkage to treatment.[43, 44, 45] Expansion of routine VL testing services has also improved programs' ability to identify unstable patients on ART.

2. ART Initiation and Management

Failed linkage from HIV testing to treatment is a leading cause of delayed ART initiation. Other systems barriers include requirements for multi-visit assessments prior to starting ART, and/or laboratory testing that may have long turn-around times and/or be unavailable. In addition to point-

of-care CD4 testing and swift preparation, several national guidelines now have streamlined visit schedules, and emphasize that availability of laboratory test results should not be a pre-requisite for starting ART.

ART Initiation

Developing rapid and early ART initiation protocols for people with advanced immunosuppression is a key element of several national strategies. Kenya's national guidelines recommend ART initiation for all people living with HIV as soon as possible, preferably within two weeks of confirmation of HIV status, and specify weekly visits until ART is initiated, twice monthly visits during the first month, and monthly visits thereafter.[46] South Africa's national guidelines recommend fast tracking ART initiation (within seven days of diagnosis) for people with CD4 cell count <200 cells/mm^3 and/or clinical stage four disease.[47] The Eswatini national guidelines recommend ART initiation, preferably within two weeks of HIV diagnosis, and encourage same-day initiation for people who are assessed as ready to start ART.[48] These guidelines further emphasize that unavailability of laboratory tests should not delay ART.

Decentralized ART services and task shifting are also important facilitators of rapid ART initiation for high-risk patients. Moving ART services closer to people living with HIV, whether to primary HF or to community settings, is a critical step towards accelerating ART access. In order to achieve such decentralization, non-specialist clinicians, such as nurses and medical officers, must be able to prescribe ART; many national guidelines now support nurse-initiated and managed ART (NIMART).

The *ICAP Approach to Differentiated Care* outlines step-by-step guidance for the management of people living with HIV (PLHIV) who present with advanced disease, defining key clinical, laboratory, and psychosocial services needed by clinic visit (Table 4) and key considerations (Table 5).

Table 4: ICAP Guidance for Patients Presenting with Advanced Disease

When	What	By Whom	Where
First Visit (Time 0)	*Clinical visit:* Confirm HIV diagnosis; CD4 test (baseline); WHO Staging; screen for CrAg and TB Adherence support and counseling *Drug:* ART and CTX initiation	Clinician$^+$	HIV Clinic
Week 2	*Clinical visit:* Management of OIs, monitor side effects/toxicity Adherence assessment, support and counseling *Drug:* ART and CTX refill for one month	Clinician$^+$	HIV Clinic
Month 1-2	*Clinical visit*: Monitor side effects/toxicity; manage OIs; initiate IPT Adherence assessment, support and counseling *Drug:* ART, INH, and CTX refill for one month	Clinician$^+$	HIV Clinic
Month 3	*Clinical visit:* Monitor side effects/toxicity Adherence assessment, support and counseling *Drug:* ART, INH, and CTX refill for one month	Clinician$^+$	HIV Clinic
Month 4-5	*Clinical visit*: Monitor side effects/toxicity Adherence assessment, support and counseling *Drug*: ART, INH, and CTX refill for one month	Clinician$^+$	HIV Clinic
Month 6 ***Milestone Visit***	*Clinical visit:* Monitor side effects/toxicity *Lab:* VL sample collection Adherence assessment, support and counseling *Drug:* ART, INH, and CTX refill for one month	Clinician$^+$	HIV Clinic

Month 7	*Clinical visit:* VL results delivered to patient**;** monitor clinical symptoms via symptom checklist and check for side effects/toxicity Adherence assessment, support and counseling Stepped up counseling and support as needed, based on VL results *Drug:* INH refill for one month, ART and CTX refill for three months	Clinician^{+}	HIV Clinic
Month 8-11	**VL>1000** *Clinical visit:* Monitor side effects/toxicity Adherence support; Stepped up counseling *Drug:* ART and CTX refill for one month *Lab:* Repeat VL between M9 and M11 after good adherence has been achieved	Clinician^{+}	HIV Clinic
	VL<1000 *Clinical Visit:* Monitor side effects/toxicity Adherence assessment, support and counseling *Drug:* ART and CTX refill for three months	Clinician^{+}	HIV Clinic
Month 12 *Milestone Visit*	*Clinical visit:* Monitor side effects/toxicity *Lab:* Second VL sample collection Adherence counseling and support *Drug:* ART and CTX refill for one month Reclassify patients as stable vs. unstable based on clinical evolution and VL results	Clinician^{+}	HIV Clinic
$^{+}$ Clinician includes physicians, nurses, clinical officers and medical technicians * At every contact with patients, HCW (clinician, nurse or lay counselor) should assess the patient and reclassify him/her as "early" or "advanced" disease, and refer to the appropriate follow-up if indicated.			

Table 5: Key Considerations for Service Delivery for People who Present with Advanced HIV Disease

Patients who Present with Advanced HIV Disease (WHO Stage 3 or 4, or CD4+ count <200cells/mL)	
Location of Service	Management at any ART service delivery point; all facility levels Initial management and ART initiation by trained and experienced HCW Consultation with MDT, TWG, mentors, and senior clinicians as needed (including telephone consultation, HIV information hotline) Referral to a higher-level facility, when feasible, if consultation is not adequate to stabilize the patient
Focus of Treatment Preparation Counseling	ART is required to prevent further damage to the immune system Starting ART soon will decrease risk of disease progression, including wasting and OIs ART is the most important treatment to restore health
Frequency of Follow- up	Weekly follow-up until ART initiation, and then at week two and four after ART initiation, and then monthly until confirmed viral suppression More frequent visits or in-patient hospitalization may be required to stabilize acute medical conditions and address psychosocial and other concerns

Switching to Second and Third-line Regimens

High-risk patients on ART may require second- or third-line ART regimens. Bottlenecks to such treatment adjustments include the lack of specialist clinicians and a situation that has engendered the use of "second-line committees" that review all proposed regimen changes and ensure specialist review and consistent application of national guidelines. Because some countries have few, or only one committee, this process can be time-consuming, and decentralizing decision-making has become a priority in a number of countries, including Lesotho, Kenya, and Mozambique.

Other barriers include the lack of familiarity with second-line regimens on the part of front line staff, who may require mentoring and supervision by more experienced clinicians. In many settings, nurses have not been trained to manage even first-line regimens, despite the implementation of NIMART in their countries of practice. For example, in a survey in Eastern Kenya, only two-thirds of nurses had been trained in comprehensive HIV care and treatment and less than half had been trained to prescribe first-line ART.[49] Innovative models to support less experienced clinicians include Kenya's Uliza! Hotline for telephone consultations[50] and pilot telemedicine programs.[51]

3. Prevention and Management of Acute Comorbidities

In contrast to stable recipients of care, whose differentiated services require fewer clinical assessments and fewer visits to HF, high-risk patients often need close follow-up by multi-disciplinary teams including specialist clinicians. Experience suggests that clinicians do not always identify high-risk patients, and that there is a need for heightened vigilance and specialized protocols to support the identification and management of these individuals.

Protocols/Procedures for High-Risk Recipients of Care

In addition to rapid and early ART initiation protocols, some programs have well-defined packages of care for patients with advanced HIV disease. In Kenya, ICAP is supporting the implementation of SIPOC, which includes standard operating protocols, checklists, and other job aids designed to support delivery of a defined set of staging, prophylaxis, and ART services (Table 6). The charts of patients with CD4 cell counts less than 100 cells/mm^3 are flagged with a SIPOC sticker, and a SIPOC patient assessment form is added to each chart. HCW are trained to be vigilant in identifying and managing high-risk patients, and facility-level supplies and equipment are defined in advance.

Table 6: The SIPOC package

Staging	Clinical staging and same-day CD4 testing
Prevention	TB symptom screening at every clinical visit; TB testing with Xpert MTB/Rif assay, TB LAM or X-ray as indicated; CrAg screening (if CD4 <100 cells/mm^3 or WHO stage 4); CPT; IPT after ruling out TB
Additional screening	Hepatitis B screening, stool for parasites, and acid-fast bacillus in anyone with persistent diarrhea
Support	Intensive follow-up (twice-monthly visits for one month after ART initiation, then monthly visits); active tracking; nutritional assessment, counseling, and supplementation; adherence counseling; linkage to peer educator with weekly phone calls

MSF has developed and implemented an approach to advanced HIV disease that identifies 'seriously ill' people living with HIV via screening and identification of danger signs associated with high mortality. They admit everyone with these signs. Immediate point-of-care tests available around the clock are conducted and include CD4, CrAg screening, TB LAM, rapid malaria test, random blood sugar, hemoglobin, and urine dipstick with additional investigations done when available. Patient management is initiated without delay with empirical treatment started for diseases where clinical suspicion is high, but where there is no diagnostic test available or where diagnostic tests cannot exclude the disease. Upon discharge from the hospital, MSF in Kenya supports the enrollment of patients into a 'Discharge Clinic' at the admission hospital where frequent intensive case-based support to the patient is provided prior to down-referral to a lower level facility.[52]

Table 7: The MSF advanced HIV package for seriously ill patients[52]

What	By Whom	Where
At the first visit, identify danger signs among PLHIV with advanced HIV disease and admit for: • Respiratory rate >30/min • Temperature >39°C • Heart rate >120/min • Systolic BP <90mm Hg • Saturation <90% • Moderate/severe dehydration • Inability to walk unaided • Altered mental state: confusion, strange behavior, reduced level of consciousness • Any other neurological problem: headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision	Clinician	Clinic
Immediate point-of-care tess and screening for OIs: CD4, CrAg screening, TB LAM, rapid malaria test, random blood sugar, hemoglobin and urine dipstick	Clinician	Hospital in patient department
Additional investigations include: Xpert MTB/Rif assay on sputum or non-sputum specimen or X-ray, abdominal ultrasound, lumbar puncture, creatinine, sodium, potassium, full blood count, VDRL, bilirubin, ALT, and blood or urine cultures	Clinician	Hospital in patient department
Initiate empirical treatment for diseases where clinical suspicion is high, but where there is no diagnostic test available or where diagnostic tests cannot exclude the disease	Clinician	Hospital in patient department

Other models of care for high-risk patients include the systematic use of case managers. For example, Kenya's national ART guidelines recommend case managers, home visits, consideration of directly-observed ART treatment, and both group and individualized counseling for recipients of care with suspected or confirmed ART failure.[46] A 2015 study in Tanzania and Zambia found that the addition of a short period of lay worker home visits to clinic-based services for patients initiating ART with fewer than 200 CD4 cells/mm^3 was associated with significantly lower mortality.[53]

Differentiating visit schedules for recipients of care with advanced disease is another approach to managing acute illness or complex comorbidities.[6] At least one study has shown that more frequent visits for patients with advanced disease leads to improved outcomes.[54] Many national guidelines recommend more intense follow-up for high-risk patients, although few specify an exact visit schedule. The *ICAP Approach to Differentiated Care* details recommended schedules for patients presenting with advanced disease and unstable patients on ART (Tables 4 and 8).

Table 8. Differentiated Care for Patients who are Unstable on ART for > 1 year

What	By Whom	Where
Clinical assessments every one to two months	Clinician+	HIV Clinic
Lab: VL monitoring three months after enhanced adherence support*	Clinician	HIV clinic
Psychosocial/Adherence support** every one to two months	Lay counselor, adherence counselor or pharmacist	HIV Clinic
Drug pick up every one to two months	Lay counselor or adherence counselor	HIV clinic
+Clinician includes physicians, nurses, clinical officers and medical technicians *Reclassify patients after each VL and/or clinical assessment **Refer to ICAP Enhanced Adherence Plan of Care		

Specialized clinics, with specific days and/or locations, are also used to support the differentiated management of high-risk patients. For example, Kenya's national ART guidelines recommend the creation of a specialized clinic day for patients on second- and third-line regimens in HF with sufficient volume. Clinics for patients with TB/HIV, Kaposi's sarcoma, cervical cancer, and other co-morbid conditions requiring specialized care and treatment are another approach; these are more common at secondary and tertiary hospitals, but are also found at less-specialized facilities, who may host a visiting specialist on specific clinic days.

Another intervention to support patients requiring intensive outpatient follow-up is the provision of temporary housing near HF for patients making frequent visits.

Prophylaxis of Opportunistic Infections

WHO guidelines recommend the use of CPT for all people living with HIV, IPT for those who screen negative for TB, and screening for Cryptococcus for those with CD4 cell counts <100 cells/mm^3. Several pilot programs go further, including SIPOC, and an initiative recently launched by Lighthouse Trust, a non-governmental organization in Malawi, which has developed a differentiated package of care for ALUP. The ALUP package will include screening for Cryptococcus with serum testing for CrAg and the addition of urine LAM (urine lipoarabinomannan) testing to TB screening protocols. Patients with CD4 cell counts <100 cells/mm^3 received an enhanced prophylaxis package used in the REALITY trial, as well as vitamins and therapeutic nutrition as needed.[36] Lighthouse has developed a flow chart for patient management and launched the ALUP services in early 2017.

Facilitating Up-Referral to More Specialized Health Facilities

Differentiated care (DC) for stable patients often includes down-referral and decentralization of care and treatment to front-line HF and to the community. Corresponding up-referral for patients who become unstable is a high-priority need. Swift identification of newly unstable patients and robust linkages to higher-level and/or more specialized care are critical for patient safety and long-term treatment success, as is accurate documentation and communication between facilities and health care providers. We found no published or grey literature examples of differentiated referral processes, however.

Linking Inpatient and Outpatient Care

Patients with advanced disease are more likely to require inpatient treatment than stable patients, making smooth referrals and linkages between inpatient and outpatient settings an essential element of high-quality care. MSF has developed and implemented an approach to advanced HIV disease, described above, that identifies 'seriously ill' people living with HIV through screening and identification of danger signs associated with high mortality. [52] They admit everyone with these signs.[52] We found no published examples of differentiated linkages processes for unstable patients.

4. Management of Co-Morbid Chronic Conditions

In some cases, high-risk recipients of care require more frequent monitoring because of chronic, not acute, health challenges. These may be HIV-related conditions, such as renal or hepatic insufficiency, or other chronic co-morbidities, such as non-communicable diseases (NCD).

Integrating HIV and NCD Services

The rising burden of cardiovascular disease (CVD), cardiovascular disease risk factors, and other chronic NCD in sub-Saharan Africa has led to dual epidemics of HIV and NCD in many countries. People living with HIV may be at higher risk of CVD than the general population, due to the effects of HIV replication on inflammatory and coagulation markers as well as the increased risk of hyperlipidemia and diabetes associated with some antiretroviral (ARV) drugs. Studies in South Africa and Swaziland, for example, show hypertension rates of 30%-40% amongst older people living with HIV enrolled in care and treatment.[55, 56] Hepatitis C, other co-infections, medications, and the direct effects of HIV can also raise the risk of renal and hepatic insufficiency amongst people living with HIV. Although integrated HIV and NCD services have been piloted in several countries, models of DC for individuals with both HIV and NCD are rare. In Kenya, MSF initiated Medication Adherence Clubs for HIV-positive patients as well as HIV-negative patients with stable hypertension and/or diabetes, providing proof of concept for the use of nurse-facilitated community-based care and treatment for mixed chronic diseases.[57] In several countries, however, patients with both HIV and NCD may receive DC for their HIV, in the form of visit spacing, multi-month prescriptions, and community-based services, but find that they must still come to a HF each month for clinical assessment and to pick up medications for NCD.

Specialized Education, Counseling, and Community Antiretroviral Groups

Although high-risk recipients of care have diverse characteristics, many share specific challenges with regards to treatment access, adherence, and retention. Designing differentiated peer education or community ARV groups is one way to provide enhanced support. Kenya's national guidelines suggest that patients on second-line ART or those not virally suppressed will benefit from co-scheduling them on specific days. This simplifies patient access to specialized clinical care, but also to specialized support groups. In some countries, community ART groups include both stable and unstable patients; in others, groups are designed specifically for unstable patients. Neither approach has undergone robust evaluation.

Enhanced adherence counseling for patients with VL>1,000 copies is recommended in many national ART guidelines. Typically, two to three EAC sessions are delivered over three months, followed by a repeat VL test. No single best approach has been identified.

Strengthening Home Care Systems

Home-based care for high-risk people living with HIV has been a staple of HIV programs for decades, although the earliest efforts focused on palliation, rather than treatment. The AIDS Support Organization (TASO) and partners conducted a cluster-randomized trial of clinic- vs. home-based ART services in rural Uganda, focusing on patients with CD4 cell counts <250 cells/mm^3 and/or WHO stage 3 or 4 disease. Home-based services included monthly visits from trained lay people who delivered ART and used a structured checklist to review adherence and check for symptoms. Counselors also visited quarterly. The home-based model was shown to be both cost-effective[58] and non-inferior to clinic based care,[59,60] even amongst patients with CD4 cell counts <50 cells/mm^3.[61] The availability of mobile health applications has expanded the possibilities for home-based care and treatment.

Summary/Way Forward

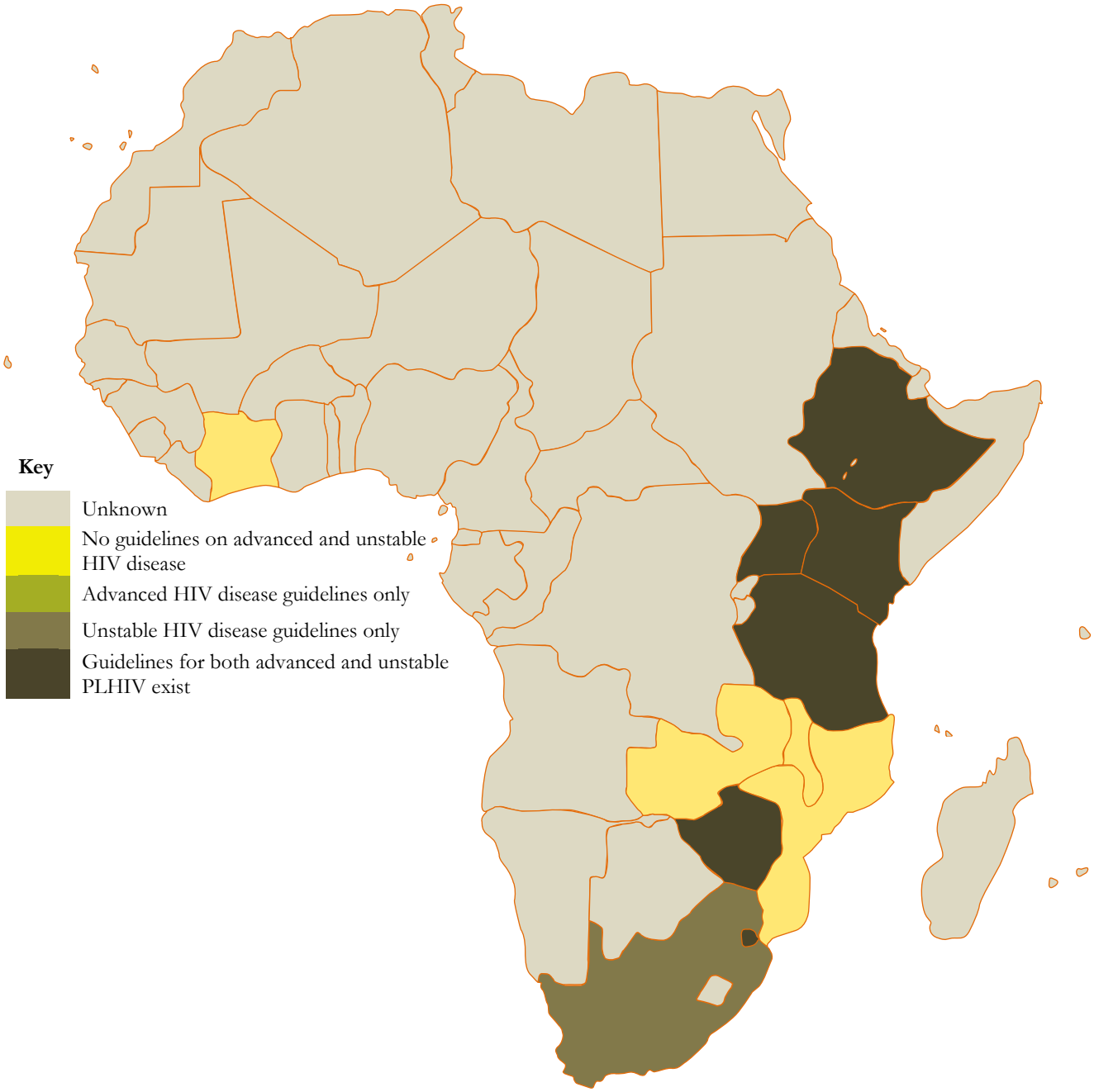
The package of care recommended for high-risk recipients of HIV care is evolving with the development of new evidence regarding the "what" of patient care. In contrast, there is limited information regarding the "how" – the optimal models of delivering these services at scale. As more and more stable people living with HIV initiate ART, the specialized needs of unstable patients and those with advanced HIV disease may be overlooked. Differentiated care for stable individuals has the potential to decompress HF, enabling HCW to provide targeted attention to people with advanced or unstable disease. However, our review indicates that guidelines, resources, and tools for DC of high-risk patients are scarce.

Programmatic priorities include ways to rapidly identify high-risk patients, such as screening and risk stratification tools. In addition, the use of standard operating protocols, clinical support tools, and job aids may ensure that unstable patients receive the appropriate level of care, as in the SIPOC program in Kenya, the MSF advanced HIV package for seriously ill patients, and the ALUP protocol in Malawi. Attention to linkages and transfers will be particularly important for high-risk patients.

Additional research priorities include exploration of *where* to deliver care for unstable patients, the extent to which this be decentralized and delivered outside of hospital settings, to determine if community-based and/or home-based models of care work for unstable patients? Although the tacit assumption may be that specialist physicians will treat high-risk patients, the *who* of DC may also be a fruitful line of enquiry. Innovative training and supervision strategies may enable non-physician clinicians to provide care for unstable patients, although this evidence base needs development.

Fostering stakeholder exchange around the issue of DC for high-risk patients is a priority for the CQUIN network, which seeks to facilitate joint learning, exchange of protocols and tools, and co-creation of program resources. Updates and resources will be available on CQUIN's website [cquin.icap.columbia.edu], in addition to related webinars and workshop reports.

Appendix A: National Guidelines of Patients at High Risk in 11 CQUIN Countries



Appendix B: Global and National Guidelines for Patients at High Risk in in 11 CQUIN Countries

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART
WHO	Consolidated Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV infections, 2015 WHO. Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy, July 2017.	**What?** • Specifies clinical package, including: rapid ART initiation, screening for CrAg, toxoplasmosis (screening method not specified) and TB, OI management if indicated, IPT if indicated, CTX prophylaxis, and "intensive follow-up" • Also mentions "desirable" services, including pregnancy testing, HBV and HCV serology, screening for STIs, and assessment for NCD **Where?** • At hospitals and decentralized primary care clinics according to the clinical status, clinical skills of the health-care workers, and access to diagnostics • Also through mobile outreach or decentralization by providing point-of-care diagnostic tests or sample transport systems • Ability to provide home visits dependent on resources and should be used where it will not increase stigma **Who?** • Clinical management: task sharing to nurses and other mid-level HCW supported through training and mentorship and with clear referral criteria and care pathways; use of community health workers (CHW) or home-based caregivers (HBC) • Diagnostics: trained and supervised non-laboratory staff, including lay HCW to perform point-of-care tests **When (visit frequency)?** • Feasibility of the visit frequency is context-specific aiming at closer follow-up during the initial period of receiving ART with rapid tracing systems for those missing appointments • Use of innovative models where face-to-face contact is not feasible, including mobile technology and CHW or HBC • Post-hospitalized follow-up patients through outpatient primary care clinic visits and home visits	***What?*** • Adherence and retention support • VL testing • Switch to second- or third-line ART if indicated • HIV drug resistance testing • OI screening and management. TB screening, diagnosis and treatment, CTX, IPT **Where?** • Not specified, but implication is at HF **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART
Cote d'Ivoire	Directives 2015 de Prise en charge des personnes vivant avec le VIH en Côte d'Ivoire (2015)	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population
Ethiopia	National Guidelines For Comprehensive HIV Prevention, Care And Treatment, 2017	***What?*** • Rapid initiation of ART (after appropriate baseline evaluation) • Systematic screening for OIs • Provision of IPT and CPT • Intensive follow-up and monitoring • Lab monitoring as per the guideline • Additional adherence counseling and support by case managers **Where?** • Hospital **Who?** • Prescriber nurse, health officer, or physician **When (visit frequency)?** • As per the national treatment guideline and may be assessed for reclassification after stabilization	***What?*** • Clinical care and lab monitoring • Additional adherence support • Timely switch to second-line ART regimen in case of treatment failure • Provide EAC and support if there is high VL **Where?** • Hospital **Who?** • Prescriber nurse, health officer, or physician **When (visit frequency)?** • Monthly and change of category if stabilized or issue settled

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART

Kenya	Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV infections in Kenya, 2018 Edition	***What?***
		• Standard Package of Care (rapid initiation of ART, CrAg screening, screening and treatment for tuberculosis, or IPT as indicated, screening for toxoplasmosis, [method not specified], CTX)
		• Intensive follow-up
		• Close monitoring for development of IRIS
		
		Where?
		• At any ART service delivery point; all facility levels, home visits may be required if unable to come to facility
		• Initial management and ART initiation by trained and experienced HCW
		• Consultation with MDT, TWG, mentors, and senior clinicians as needed (including telephone consultation such as Uliza! Clinicians' HIV Hotline)
		• Referral to a higher-level facility when feasible if consultation is not adequate to stabilize the patient
		
		Who?
		• Initial management and ART initiation by trained and experienced HCW
		• Consultation with MDT, TWG, mentors, and senior clinicians as needed (including telephone consultation such as Uliza! Clinicians' HIV Hotline)
		• Referral to a higher-level facility when feasible if consultation is not adequate to stabilize the patient
		
		When (visit frequency)?
		• Weekly follow-up until ART initiation, and then at week two and four after ART initiation, and then monthly until confirmed viral suppression
		• More frequent visits or hospitalization may be required to stabilize acute medical conditions and address psychosocial and other concerns
			What?
			• Enhanced Adherence Counselling (EAC)
			• Enhanced Adherence Support Interventions (for patients failing or at high-risk of failing treatment)
			• Directly Observed Therapy (DOT) for patients with suspected/confirmed treatment failure
			• Special Support Groups for patients who failing treatment or who are on second-line ART.
			• Treatment preparation for second-line or third-line ART
			• Targeted counselling and education to prepare them for the new regimen and to support ongoing adherence
			• Organization of patients on second-or third-line ART to be booked on the same day and seen by a dedicated MDT clinic.
			
			Who?
			• Clinician not specified, but notes that management of unstable patients on ART is multifaceted and may include:
			  ○ Care giver
			  ○ Family member
			  ○ Treatment buddy
			  ○ Case manager
			  ○ Special support groups such as putting patients with similar challenges into peer-support groups
			  ○ Community support groups (CHWs, VHW)
			  ○ MDT
			• Referral to a higher-level facility if consultation is not adequate to stabilize the patient
			
			Where?
			• Any ART service delivery point; all facility levels
			
			When (visit frequency)?
			• Patients with detectable VL should have DOTs to confirm good adherence for three months before repeating the VL.
			• Every one to three months, based on clinical judgment and the specific reason/s they have not met stable eligibility criteria
			• Additional visits as required to address any medical or psychosocial concerns

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART
Malawi	Malawi Guidelines for Clinical Management of HIV in Children and Adults (2016)	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population
Mozambique	Modelos Diferenciados de Serviços em Moçambique, 2018 Estratégia de Grupos de Apoio e Adesão Comunitária, 2015	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population	***What?*** • No specific guidance for this population **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART

South Africa	National Consolidated Guidelines for the Prevention of Mother to Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults, 2015	***What?***
		• No specific guidance for this population
		
		Where?
		• No specific guidance for this population
		
		Who?
		• No specific guidance for this population
		
		When (visit frequency)?
		• No specific guidance for this population
			What?
			• For patients with <80% adherence at any visit and those with first VL>1000 copies/ml.
			  ○ The ART counsellor/nurse or doctor re-educates the patient, caregiver, and their 'buddy' about the importance of adherence
			  ○ Evaluation of the support structures in place and how they can be improved; Encouraging patients to participate in a support groups
			  ▪ Assessment for mental health issues/substance misuse
			  ○ Investigating the family situation through a social worker and actively address food security
			
			Where?
			• Increasing home visits by therapeutic counsellors/patient advocates to daily or weekly at a minimum
			
			Who?
			• There is third-line review committee set up to coordinate the management of patients failing on the second-line regimen.
			
			When (visit frequency)?
			• No specific guidance for this population

Eswatini	Swaziland Integrated HIV Management Guidelines, 2018	***What?*** • Rapid ART initiation (within seven days) • Intensive monitoring of clinical response, development of IRIS, non-adherence to ART • Enhanced psychosocial counselling and adherence support • Additional laboratory tests: CrAg screening for all clients with CD4 ≤100 cells/mm^3 and LF TB-LAM testing for HIV-positive, TB-presumptive clients with CD4 ≤100 cells/mm^3 or seriously ill with danger signs. **Where?** • HF	***What?*** • Stepped-up adherence counselling • If there is evidence of treatment failure timely switching to second- or third-line regimen is necessary • Advanced immunodeficiency package (if CD4 <200) • Management of other comorbidities and adverse drug reactions to common first-line ARV • Special clinic days for clinically unstable clients e.g. targeting clients suspected to be failing treatment • HIV index testing • Provision of condoms

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART

		Who?
		• Nurses, doctors, expert clients, laboratory teams, pharmacy teams
		
		When (visit frequency)?
		• Soon after HIV diagnosis
		  ○ ART initiation within two weeks to one month
		  ○ CTX from enrolment
		  ○ IPT from one month post-ART initiation
		• ART refill:
		  ○ After initiating ART: two weeks
		  ○ First six months on ART: every one month
		  ○ Refill after sixmonths will be dependent on the VL result
			Where?
			• HF
			
			Who?
			• Multi-disciplinary team
			
			When (visit frequency)?
			• Clinical assessment:
			  ○ Every 1 month, or frequently as needed
			• ART refill:
			  ○ At least every one month
			  ○ Special clinic days e.g. Pediatric Days, specific days for clients completing SUAC sessions

Tanzania	HIV Service Delivery Models: Mapping HIV Service Delivery Strategies in Tanzania in 2017.	***What?*** • Rapid initiation of ART (once the risk of IRIS is ruled out); • Systematic screening for CrAg if CD4+ < 100 cell/mm^3; • Screening and treatment for TB or provision of IPT as needed; • Provision of CPT; and • Increased intensity of follow-up during the first few months **Where?** • At all facility levels at any ART service delivery point • Referral to a higher-level facility when feasible if consultation is not adequate to stabilize the client	***What?*** • Case management to address reason/s for not meeting stable eligibility criteria • Enhanced adherence counselling should be available both at facility and community level • VL monitoring according to the national algorithm • Appropriate switch to second-line ART **Where?** • All facility levels • Referral to a higher-level facility when feasible if consultation is not adequate to stabilize the client **Who?** • Trained HCW

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART
		Who? • Trained HCW (doctor, AMO, clinical officer, nurse) **When (visit frequency)?** • ART initiation should take place preferably within two weeks of a positive HIV test, unless there is a medical contraindication or psychosocial contraindication • Weekly follow-up until ART initiation, and then at week two and four after ART initiation, and then monthly until the patient is stable • More frequent visits or hospitalization may be required to stabilize acute medical conditions and address psychosocial and other concerns	**When (visit frequency)?** • Every month based on clinical judgment and the specific reason/s stable eligibility criteria have not been met • Additional visits as required to address any medical or psychosocial concerns • The decision to switch to second-line should preferably take no longer than two weeks from the receipt of the second-high VL>1000 copies/mL
Uganda	Consolidated Guidelines for Preventing and Treating HIV Infections in Uganda, *Draft 2016*	***What?*** • Rapid initiation of ART • OI screening, e.g. CrAg • Nutrition screening • NCD • History taking and physical examination (vital signs including weight, blood pressure) • Other tests as indicated • Adherence support **Where?** • Clinical care in facility, with adherence support at both facility and community **Who?** • Clinician (medical officer, i.e. MO; clinical officer, i.e. CO; nursing officer) • Refills: dispenser /nurse / trained lay providers (expert client) • Adherence support: counsellor/ nurse/ trained peer **When (visit frequency)?** • Monthly	***What?*** • OI screening, e.g. CrAg • Nutrition screening • NCD • History taking and physical examination (vital signs including weight, blood pressure) • Other tests as indicated • Adherence support **Where?** • Clinical care in facility, with adherence support at both facility and community **Who?** • Clinician (medical officer, i.e. MO; clinical officer, i.e. CO; nursing officer) • Refills: dispenser /nurse / trained lay providers (expert client) • Adherence support: counsellor/ nurse/ trained peer **When (visit frequency)?** • Monthly

Country	Title of Guideline(s)	Recommendations for Patients Presenting w/ Advanced Disease	Recommendations for Unstable Patients on ART
Zambia	Zambia Consolidated Guidelines for Prevention and Treatment of HIV Infection 2018	***What?*** • No specific guidance for this population ***Where?*** • No specific guidance for individuals presenting with advanced disease, but clearly describes levels of referral ***Who?*** • No specific guidance for individuals presenting with advanced disease • Certified nurse/midwives can prescribe first-line ART ***When (visit frequency)?*** • No specific guidance for this population	***What?*** • No specific guidance for this population ***Where?*** • Advanced Treatment Centres (ATCs) should manage complex and advanced patients, including those failing second-line ART; can also provide consultations to clinicians at other levels of the health system ***Who?*** • Diverse cadres can prescribe second-line ART with appropriate training and supervision (nurse prescribers, clinical officers, medical licentiates, medical officers); only medical specialists can prescribe third-line ART. ***When (visit frequency)?*** • No specific guidance for this population
Zimbabwe	Operational and Service Delivery Manual for Prevention, Care and Treatment of HIV in Zimbabwe, 2015	***What?*** • Basic HIV and ART education and rapid ART initiation • Clinical readiness: including assessment of clients with advanced disease (including screening for cryptococcal disease if CD4 is <100 cells/mm^3) • Psychosocial readiness assessment • Treatment plan **Where?** • Primarily at the facility • Where mobile outreach is being performed regularly to a site, ART initiation may also be considered **Who?** • Trained HCW (doctor, AMO, clinical officer, nurse) **When (visit frequency)?** • Fortnightly for one month then monthly until six months. Thereafter the visits are dependent on the VL results	***What?*** • The client should be referred to the appropriate differentiated intervention: enhanced adherence counselling pathway, treatment of TB, or integrated PMTCT/ANC until they again meet the eligibility criteria for stable clients • Devising an action plan for clients with a first VL (targeted or routine) more than 1000 copies/ml • Assessment of OIs • Home visits and/or community support • Assigning a "treatment buddy" • Establishing 'Clinic Case Discussion" meetings • Counseling preparation for second-line **Where?** • No specific guidance for this population **Who?** • No specific guidance for this population **When (visit frequency)?** • No specific guidance for this population

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