University of Zimbabwe
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Patients with Advanced HIV Disease

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ICAP Webinar

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Disclosures

- No disclosures

Guidance Documents

- Consolidated guidelines on when to start ART-WHO 2016.
- Managing Advanced HIV Disease and Rapid Initiation of ART, July 2017.
- Differentiated Service Delivery for Adults at High Risk of HIV Disease Progression. A Call to Action. ICAP, 2017.
- ICAP Approach to Differentiated Care, 2017.

Outline-Advanced HIV Disease

- Background/Rationale
- Patients with Advanced HIV Disease
- Major causes of Mortality and Morbidity
- Management of Patients with Advanced HIV Disease
- Treatment of Co-Morbid conditions
- Antiretroviral therapy
- The How of care of Patients with Advanced HIV Disease
- Conclusions

Background/Rationale

- The scale up of ART is one of the world's greatest public health success stories
- PLH on ART in 2003-400,000; by 2017 the number went up to 22 .9 million
- Number of deaths averted by ART scale up-7.8 million
- HIV infection has dropped by 35% since 2000 through prevention and treatment services

Braistein Lancet 2006, Keiser PLoS Med 2008, Castelnuovo CID 2009, Lawn SD. AIDS 2008;22;1897,

Challenges in HIV/AIDS Service Delivery

- Changing guidelines
- Ambitious global targets
- Rapid expansion of people eligible for ART
- To meet 90-90-90 targets the number will need to be doubled by 2020
- Global funding has plateaued
- Overcrowded health facilities
- Sub-optimal retention rates

DSD for Adults at high risk of HIV progression. Call to Action. ICAP2017

Differentiated Service Delivery (DSD)

- DSD is a patient-centred model of care that aims to enhance quality, efficiency and patient satisfaction while maintaining the principles of the public health approach
- Examples include
  - Fast-track appointments
  - Multi-month ART prescribing
  - Decreased visit frequency
  - Community based-ART groups
  - Etc.

Duncombe C. Trop Med Int Health 2015; El-Sadr. AIDS 2016

Advanced HIV Disease-Definition

- WHO (2016 Consolidated ARV Guidelines)
  - Adults & adolescents & Children above 5 years
    - CD4 count <200 cells/mm^3 or WHO stage 3 or 4 event
  - All HIV infected children below 5 years

1. WHO 2016 guidelines 2. Managing Advanced HIV Disease & rapid initiation of ART July 2017

ICAP overview of Patient classification For Differentiated Care. (ICAP Approach to Differentiated Care 2017)

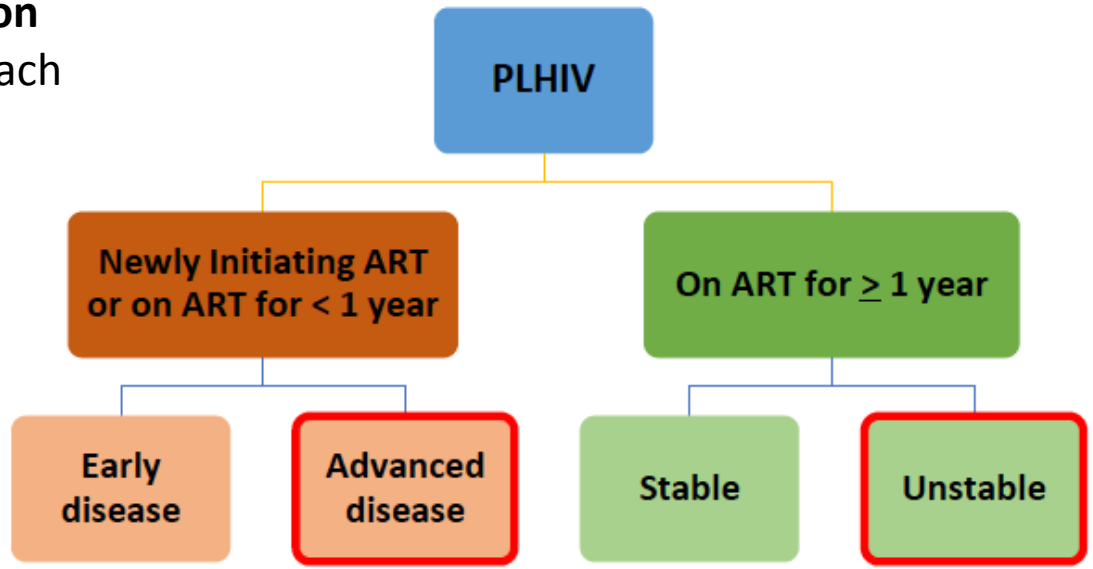


Table 1: Defining High-Risk Patients

New to ART / Advanced Disease	On ART for > 1 year / Unstable
Newly initiating ART or on ART for <1 year and	*On ART for >1 year and any of the following:*
CD4 <200/mm^3 and/or	Not virally suppressed*
WHO stage III/IV	CD4 <200/mm^3
	Adverse drug reaction requiring ongoing monitoring
	Active opportunistic infection, including TB
	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 6 months
**Non-adherent = 2+ missed doses a month for patients on once-daily regimens, 4+ missed doses a month for patients on twice-daily regimens; and/or misses drug pickups

Advanced HIV Disease

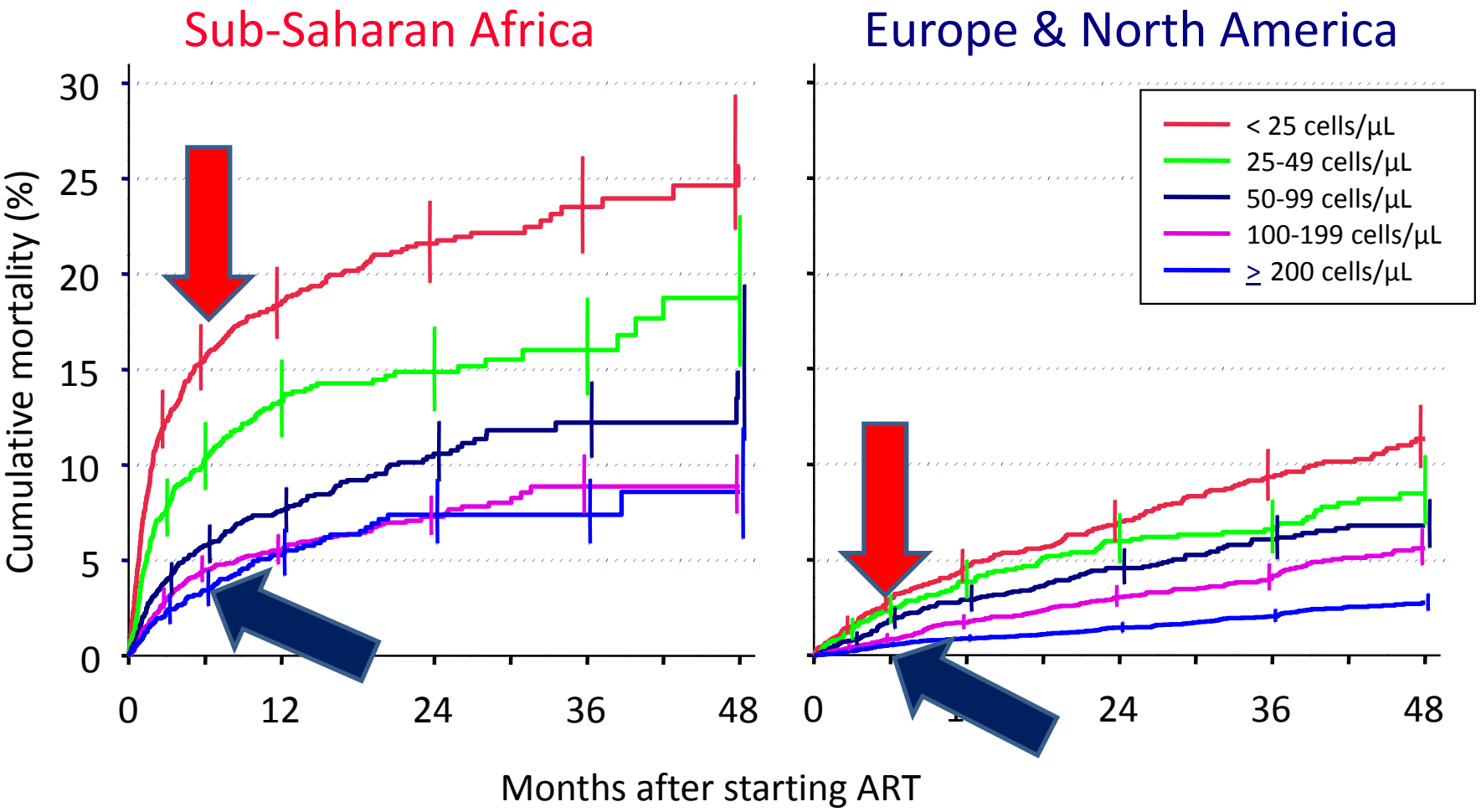
- High risk of mortality and morbidity
  - Worse with CD4 <50 cell/mm^3
- Less robust CD4 recovery on initiating ART
- High risk of OIs

1 Year Mortality
50 published cohort studies by region

Cohort	Mortality proportion, median (range)
Sub-saharan Africa (n=35)	17% (11-24%)
Asia (n=5;China, Cambodia, Thailand)	11% (10-13%)
Americas (n=2; Haiti, Peru)	7% (1%-20%)
Multiregional (n=5; Asia including India, Africa, South America, Caribbean)	8% (6-10%)

Gupta et al PLOS One 2011

Mortality by baseline CD4 cell count (ART-LINC and ART-CC)



Causes of early mortality after initiating ART

- Tuberculosis
  - Main cause of mortality among patients initiating ART
- Bacterial sepsis
  - Septicaemia, pneumonia, GI infection, CNS infection, other
- Cryptococcal meningitis
  - Cryptococococaemia leads to meningitis
  - Less common in children < 5 years
- Pneumocystis jirovecii pneumonia
- Malnutrition
- Wasting syndrome

Gupta R. AIDS 2015; Ford N. J Int AIDS Soc 2016; Ford N, Lancet HIV. 2015; Rajasingham R. Lancet Infet Dis; Park B. 2009 Wang ZD.

Causes of early mortality after initiating ART

- Other
  - Toxoplamosis
  - Cytomegalovirus infection
  - Histoplasmosis
  - Talaromycosis (penicilliosis)
  - Kaposi’s sarcoma
  - Gastrointestinal infections
  - Renal failure

Le T. CID 2011; Hu Y. Myopathologia 2013

Management of Advanced HIV Disease

- Identification of Advanced HIV Disease
- Screening for major diseases causing morbidity and mortality
- Prophylaxis and pre-emptive therapy
- Antiretroviral therapy initiation

Package of Care-Advanced Disease

- Achieving immune system recovery with ART is the primary way to reduce morbidity and mortality in HIV disease
- Prompt initiation of OI prophylaxis
- Screening and treatment of co-morbidities
- Swift initiation of ART (if no Crypto)
- Follow-up & monitoring
  - Adherence
  - Adverse drug reactions
  - IRIS

Table 1 Components of the package of care for people with advanced HIV disease

	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]

Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[b]	≤350 cells/mm³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Annex 1
	TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm³	Yes	Yes	Not applicable (screening not advised)

Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
	[illegible]				
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	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

Antiretroviral therapy initiation

- ART Treat All
- Need to start early
- Rapid initiation of ART
  - Issues of patient readiness-psychological and logistical
  - Screening for OIs
  - Need to start ART early
- Rapid ART initiation
  - Within 1 week of HIV diagnosis or eligibility determination
  - Same-day start of ART
- Who will provide ART-NIMART
- Adherence/adherence support
- Loss to follow-up

REALITY Trial

ART-naïve HIV-infected adults & children >5 years with CD4<100 cells/mm^3

Initiated ART and randomised 1:1

Enhanced prophylaxis: CTX* +
- 12 weeks INH/B6* 300/25mg/d (anti-TB)
- 12 weeks fluconazole 100mg/d (anti-fungal)
- 5 days azithromycin 500mg/d (anti-bacterial & anti-protozoal)
- single-dose albendazole 400mg (anti-helminth)

Standard prophylaxis: CTX *(most received additional INH/B6* from 12 weeks depending on national guidelines)*

***INH/B6/CTX scored FDC**
Half doses if <12 years

- Follow-up to week 48
  - **Safety bloods** at screening, weeks 4 and 48; **FBC & CD4** at weeks 0, 12, 24, 36, 48; **Viral loads** retrospectively at weeks 0, 4, 12, 24, 48
- Two other factorial randomisations investigated
  - 12 weeks adjunctive raltegravir (**FRAB0102LB**)
  - 12 weeks supplementary food
- **Primary endpoint: 24-week mortality**

Hakim J. NEJM 2017

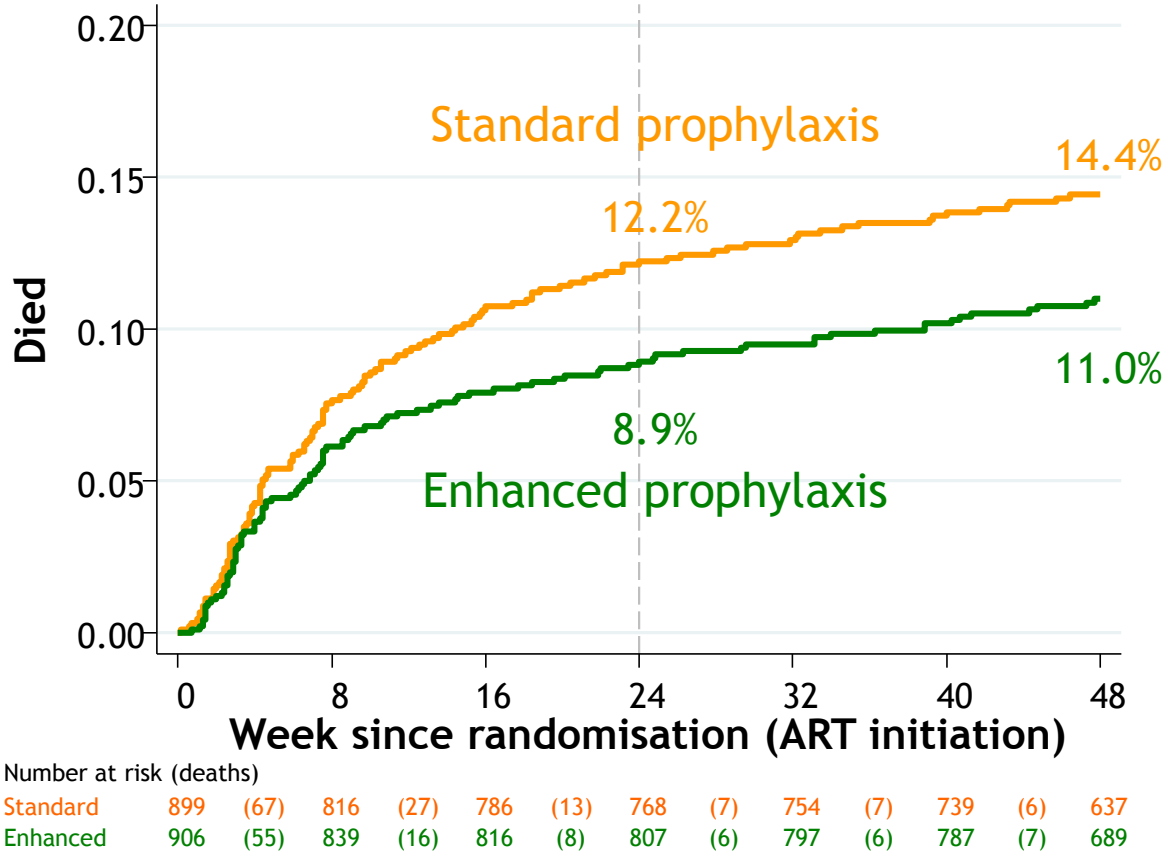
Baseline characteristics (N=1805)

n (%) or median (IQR)

Characteristic	Enhanced Px (N=906)	Standard Px (N=899)
Male	477 (53%)	484 (54%)
Age (years)	36 (29-42) [6-71]	36 (30-42) [5-78]
5-17 years	39 (4%)	33 (4%)
Current TB disease	122 (13%)	125 (14%)
WHO stage 1 or 2	436 (48%)	418 (46%)
CD4 (cells/mm^3)	38 (16-64)	36 (16-60)
0-24 cells/mm^3	323 (36%)	333 (37%)
VL (c/ml) (N=1568)	229,690	230,540
>100,000 c/ml	574/782 (73%)	563/786 (72%)
EFV-based ART	820 (91%)	799 (89%)
TDF/FTC NRTI backbone	716 (79%)	706 (79%)

Results: All-cause mortality

- Mortality at 24 weeks: 8.9% enhanced Px vs 12.2% standard Px



w24: **HR=0.73**
(95% CI 0.54-0.97)
p=0.03

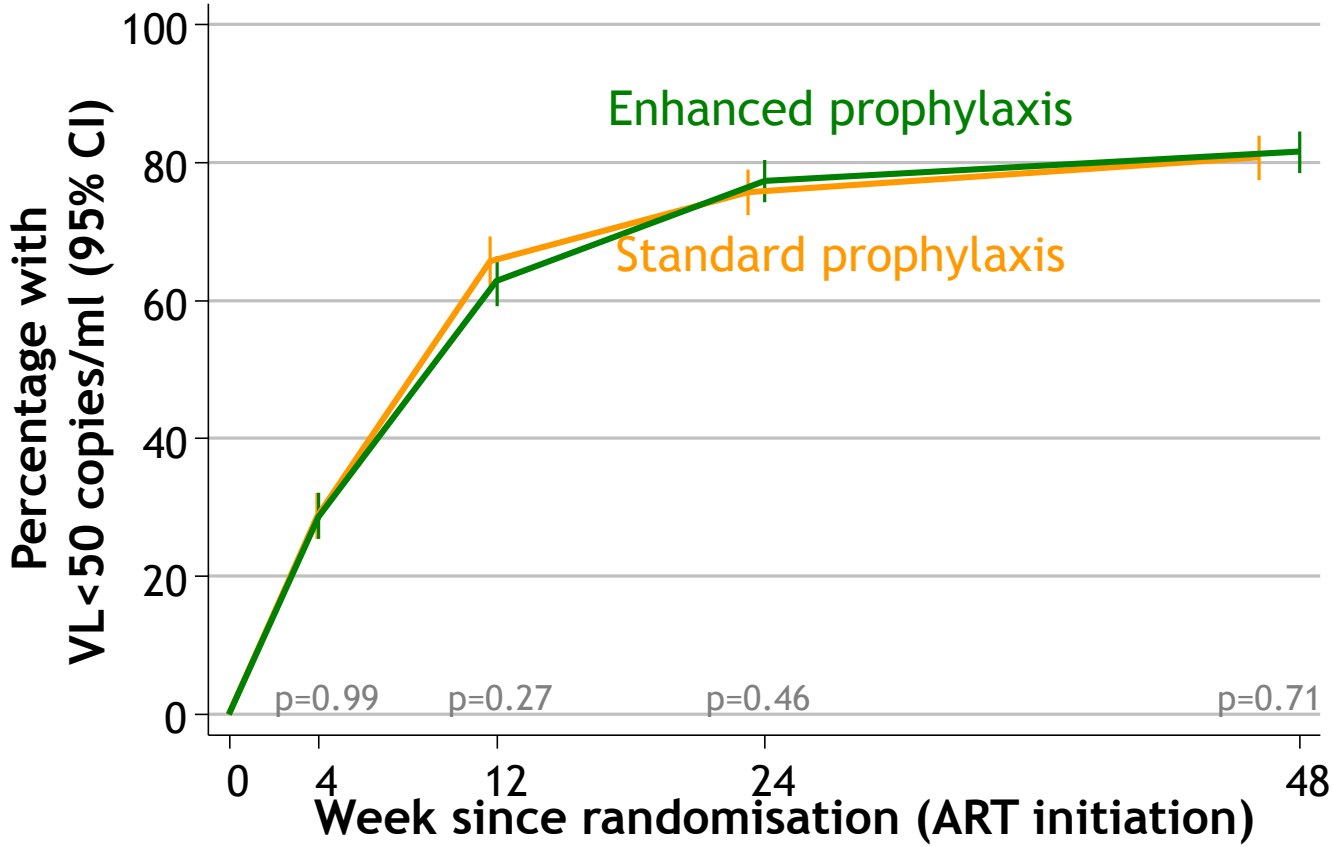
w48: **HR=0.75**
(95% CI 0.58-0.98)
p=0.04

3.3 lives saved for every 100 treated
NNT=30

- 56 (3.1%) lost to follow-up at 48 weeks
- 0-12w: 93% vs 14% on isoniazid and 95% vs 3% on fluconazole (Px or Rx)
- No interactions with other randomisations (p>0.8)

VL (& ART adherence)

- No evidence of difference in VL suppression (GEE p=0.75)



- No evidence of difference in CD4 reconstitution (GEE p=0.55)

Conclusions

- In HIV-infected adults/children with CD4<100 cells/mm^3
  - **Enhanced prophylaxis** at ART initiation
    - Reduced early mortality from 12.2% to 8.9% (25% relative reduction, 3.3% absolute reduction)
    - Reduced adverse events and hospitalisations
- The additional pill burden did not adversely affect VL suppression and was decreased by a well-accepted FDC of CTX/INH/B6 (WHO pre-qualification in progress)
- Policy-makers should consider adopting and implementing this low-cost broad infection prevention package which could **save 3.3 lives for every 100 individuals treated**

The “How” of care for patients with Advanced HIV Disease

- How should these packages of care be delivered?
- In an ICAP review key challenges and barriers were identified for high risk patients

DSD for Adults at high risk of HIV progression. Call to Action. ICAP2017

Table 3: Key challenges and barriers to service delivery for high-risk patients

Challenge	Illustrative Barriers/Challenges
Identification of high-risk patients	Delayed ART eligibility assessment
	Delayed identification of failing regimens
	Delayed linkage from testing to treatment
ART initiation and management	Delayed switch to 2nd/3rd line regimens
	Lack of standard operating protocols (SOPs) for high risk patients
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

DSD for Adults at high risk of HIV progression. Call to Action. ICAP2017

Innovations of DSD services for high risk patients

- Severely immunosuppressed package of care (SIPCO)-Kenya
- Advanced, Late and Unstable patients (ALUP)-Malawi
  - Also delivers the REALITY package
- Models in the SEARCH study in Uganda

Conclusions

- Patients with advanced HIV disease
- Package of care should be implemented
- Early identification
- Screening for common causes of morbidity and mortality
- Pre-emptive treatment and specific treatment for opportunistic conditions
- Rapid ART initiation
- Several research gaps exist both in the “what” and “how” to manage these patients

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Thank you