The CQUIN Learning Network

Differentiated Care for Patients at High Risk of HIV Disease Progression

Patients at High Risk of Disease Progression: Global Best Practices

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KNOWLEDGE • DILIGENCE • INTEGRITY

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HIV LEARNING NETWORK
The CQUIN Project for Differentiated Care

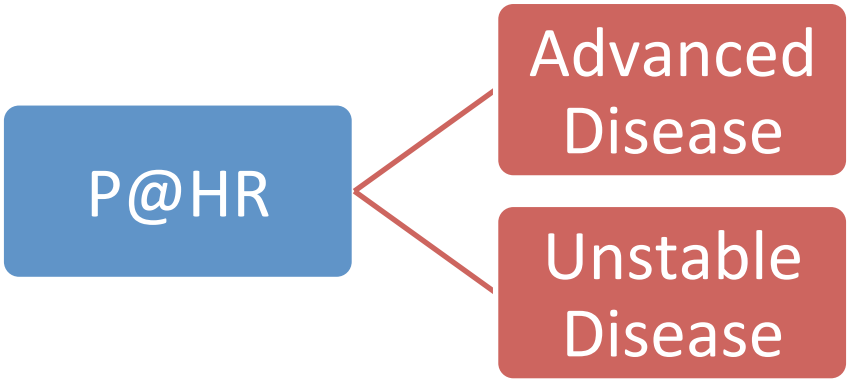
ICAP
GLOBAL. HEALTH. ACTION.
Columbia University
Mailman School of Public Health

Disclosures

- None

Patients at High Risk

- Patients at high risk:
  - Disease progression
  - Poor outcomes



P@HR

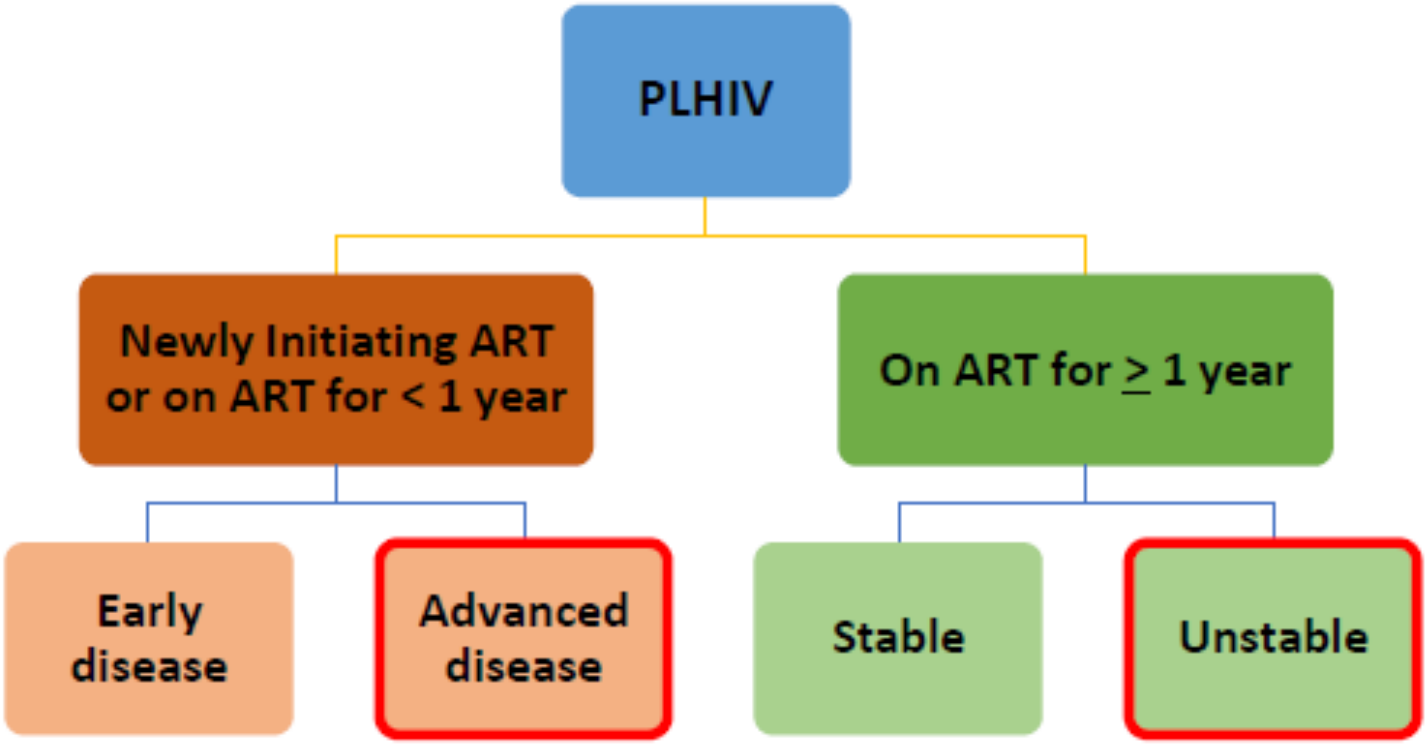
Table 1: Defining High-Risk Patients

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

Overview of Patient Classification for DC-ICAP



Models of Care for P@HR of Poor Outcomes

- “the what”-package of care
- “the how”-programmatic models

Advanced Disease-Rationale

- CD4 <200 cells/mm^3
  - High risk of mortality
  - Worse if CD4 <50cells/mm^3
- With advanced disease there is less robust CD4 count recovery
  - High risk of OIs especially TB

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

Packages of Care

- Cotrimoxazole
- TB
  - Screen and treat
  - IPT
  - GeneXpert and LAM
- Cryptococcal infection
  - Screen CD<100 and pre-emptive Rx with fluconazole

Models of Packages of Care for Advanced Disease

- WHO-2016
  - Rapid initiation of ART
  - Screening for Crypto in blood
  - Screen for TB-Rx or IPT
  - Cotrimoxazole
  - Intensive follow-up
- Updated guidelines
  - July 2017
- ICAP
  - Intensive management of any presenting illness
  - Close monitoring for IRIS
  - Ongoing adherence counselling
- REALITY STUDY PACKAGE
  - Presented in Durban July 2016
    - NEJM Wed 20 July 2017

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**

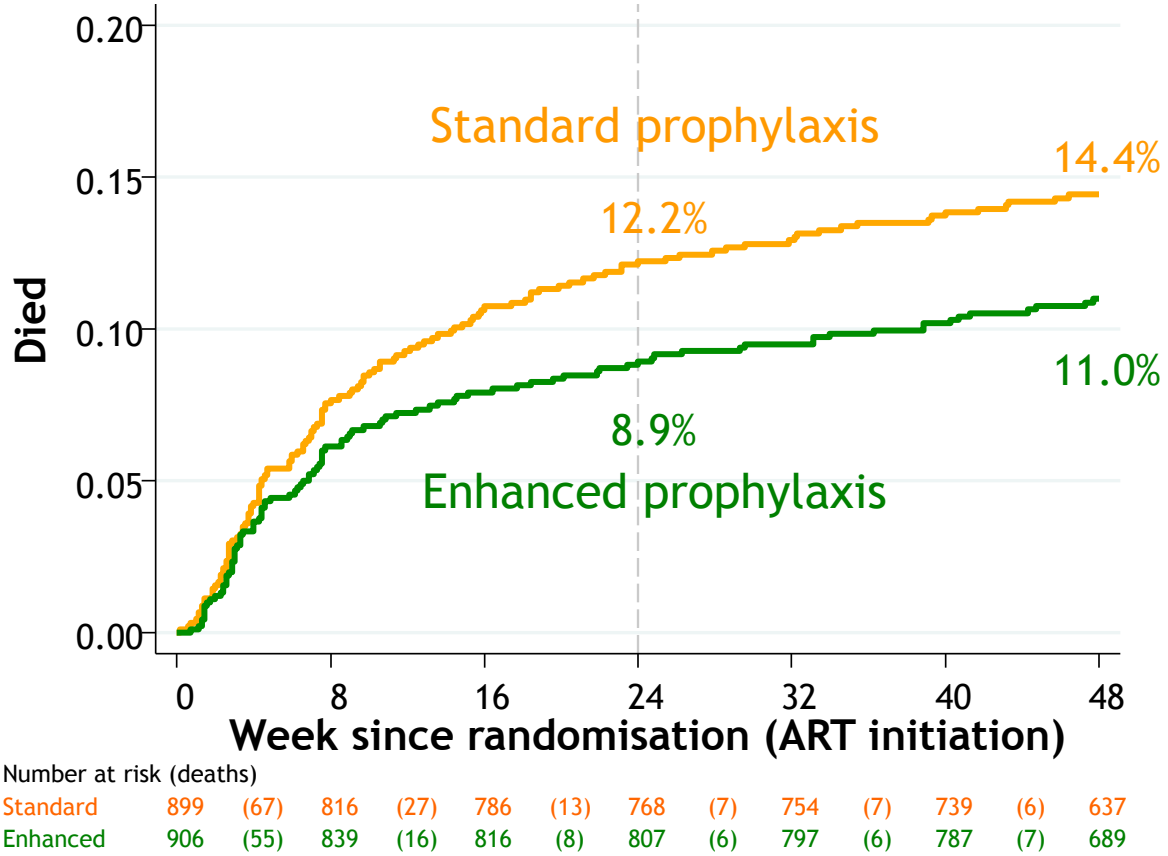
Baseline characteristics (N=1805)

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

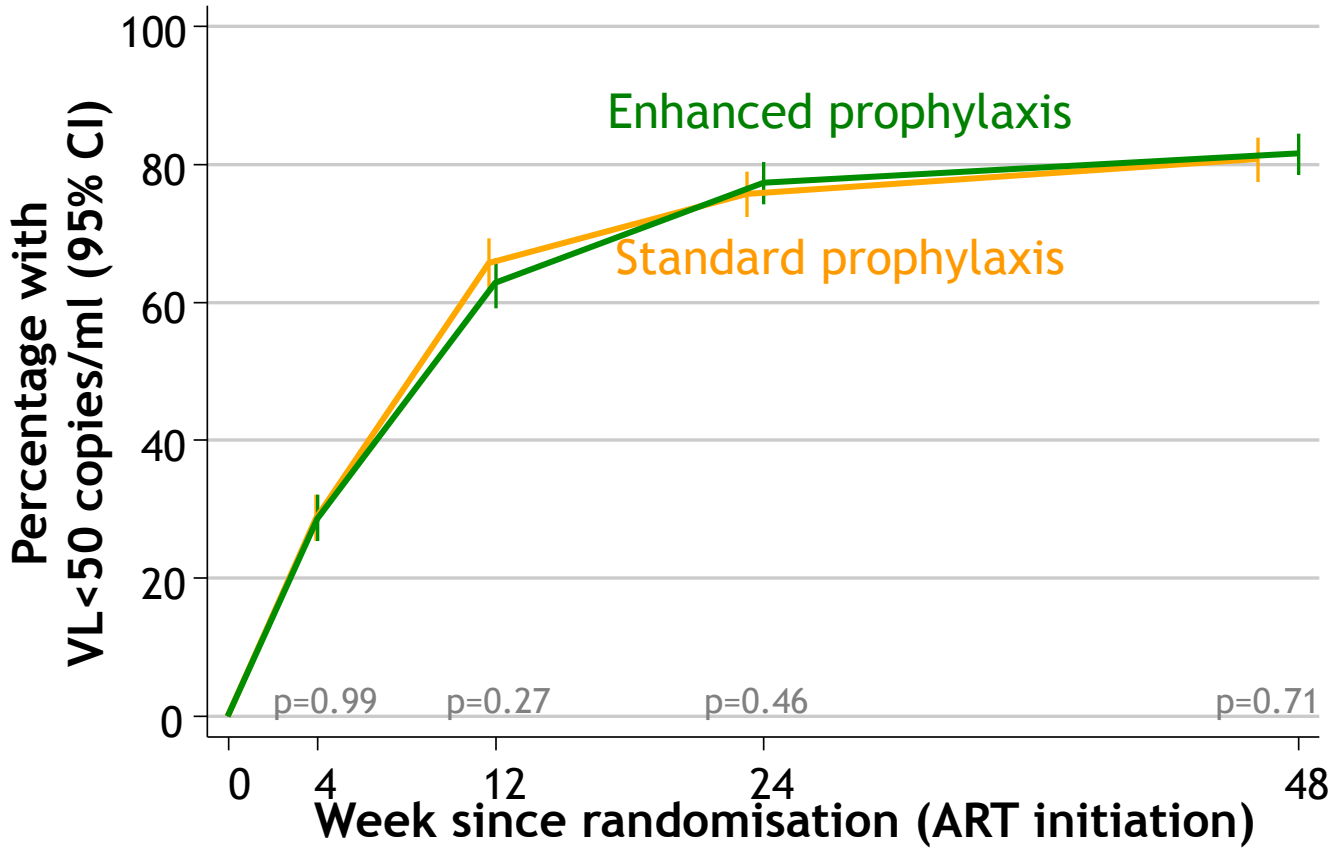
w48: **HR=0.75**
(95% CI 0.58-0.98)
p=0.04

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**

Unstable Patients

On ART for > 1 year / Unstable
On ART for >1 year and any of the following:
Not virally suppressed*
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

High risk of drug resistance mutations

- Mixed group of patients
- ↑Risk of poor clinical outcomes including complications + treatment failure
- ↑Risk of Ois
- Mental illness
- Substance use
- Comorbid conditions
- Cardiovascular, renal, hepatic
- Enhanced adherence to ART

Unstable Patients-Package of Care

- Intensive/advanced clinical care
  - Treatment if OIs, drug reactions, co-morbidities
- Enhanced adherence support
  - Frequent VL and CD4 monitoring (often non-adherent patients)
- Advanced ART management
  - Drug resistance
- Overarching elements
  - Frequent visits, specialist care, intensive psychosocial and adherence support

How is care delivered to P@HR of Disease Progression-issues to consider

- Timely identification of P@HR
- ART initiation & management
- Switching to 2^{nd}/3^{rd} line regimens
- Prevention and management of acute co-morbidities
- Protocols/procedures for P@HR
- Prophylaxis for OIs
- Up-referral
- Inpatient and outpatient treatment link
- Integration of HIV and NCD services
- Specialized Education, counselling, community services
- Strengthening home care systems

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Thank you