HIV TREATMENT

HIV/AIDS Department

# The Early Release Guidelines on When to start antiretroviral therapy and on pre-exposure prophylaxis for HIV


Meg Doherty & Bob Grant

5 Oct 2015

AVAC Webinar

World Health Organization

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# Acknowledgements

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Special thanks to all the external experts who contributed as members of the Guideline Development Groups, and to those who contributed to the GRADE systematic reviews and supporting evidence which informed the guidelines process.

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**IeDEA Collaboration**

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**PEPFAR**

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# 2015 WHO Consolidated ARV Guidelines

**WHAT TO DO?**

- When to start
- What to use for children, adolescents, pregnant women
- How to monitor
- Co-infections
- HIV and MH & NCDs
- PrEP, PEP

**Clinical**

**Operational & Service Delivery**

**Programmatic Prioritization**

**HOW TO DECIDE?**

- Approaches to prioritization & sequencing
- Tool kits for country adaptation and implementation

**HOW TO DO IT WELL?**

- Care Packages (Differentiated /Adaptive Care)
- Linkages, Retention, Adherence
- Quality of care
- Diagnostics
- Supply chain

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# 2015 ARV Guidelines Process

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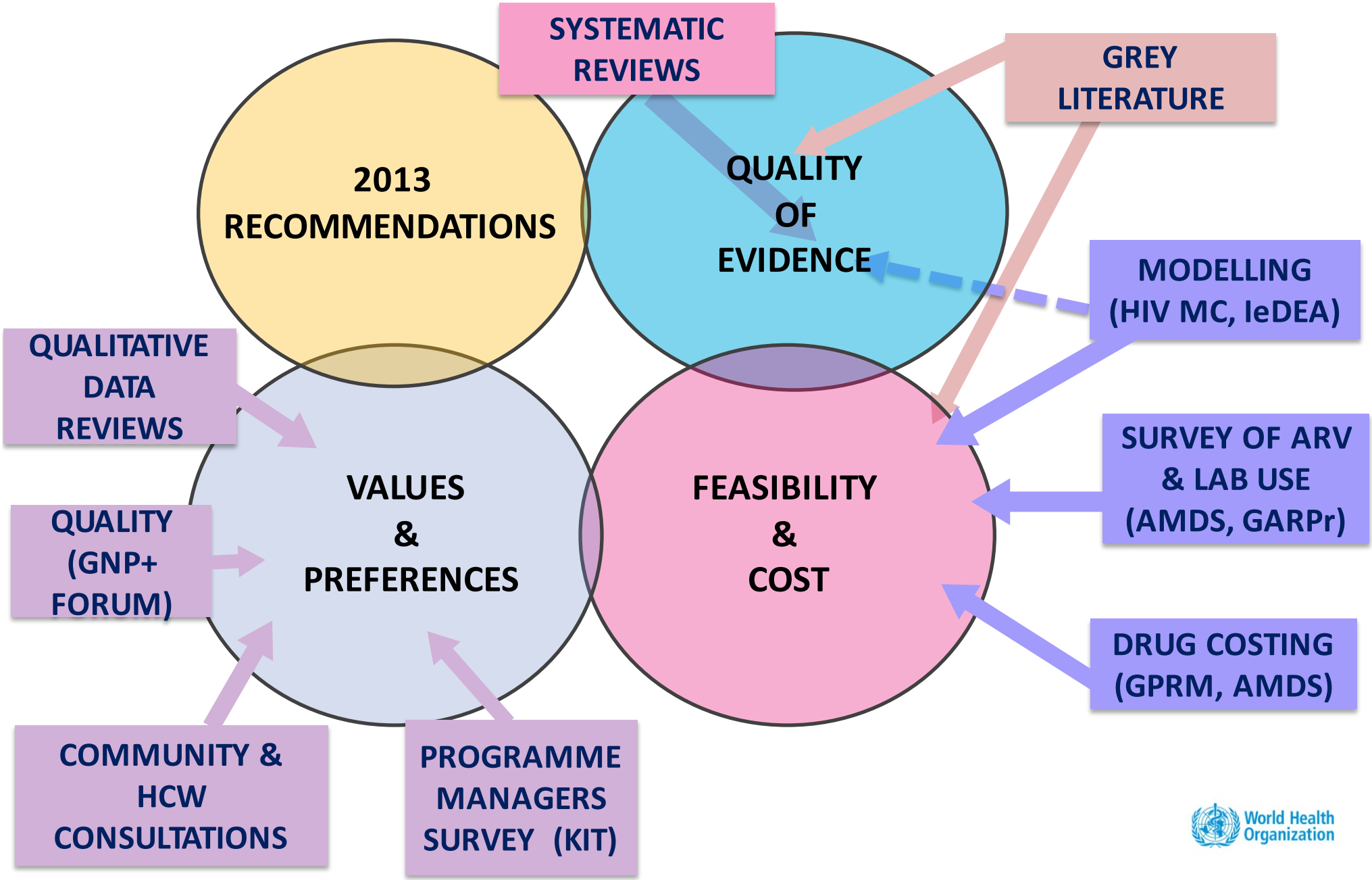


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# ART eligibility: 5 policy scenarios



## Estimated millions of people eligible for ART (2014)

30 m. 36.9 m.

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| CD4 ≤ 200 | CD4 ≤ 350 | CD4 ≤ 350 + TasP | CD4 ≤ 500 | All HIV+ |
| Recommended since 2003 | Recommended since 2010 | Incremental approach 2012 | + indications for ART at any CD4 | Treat ALL |
| | | | 2013 guidelines | 2015 guidelines |

## WHEN TO START - 2015 RECOMMENDATIONS

| Target Population | Specific Recommendation | Recommendation Strength | Quality of Evidence |
|---|---|---|---|
| Adults | ART initiation at any CD4 | Strong | Moderate NEW |
| | ART initiation if WHO clinical stage III/IV or CD4 ≤ 350 as priority | Strong | Moderate |
| Pregnant/BF women | ARV initiation at any CD4 and continued lifelong (Option B+) | Strong | Moderate REVISED |
| Adolescents | ART initiation if 10-19 years-old | Conditional | Low NEW |
| | ART initiation if WHO clinical stage III/IV or CD4 ≤ 350 as priority | Strong | Moderate |
| Children | ART initiation if 1-10 years-old | Conditional | Low NEW |
| | ART initiation if < 1 year-old | Strong | Moderate |
| | ART initiation if < 2 years-old or WHO clinical stage III/IV or CD4 < 25% (< 5 years) or ≤ 350 (>5 years) as priority | Strong | Moderate |

# Evidence Summary: When to Start in Adults

- **Systematic Review of 18 eligible studies** (1 RCT and 17 observational cohorts )
- Some observational studies reported **results from a single cohort** (6 studies)

- **Outcomes reported:**

  - ✓ **Mortality**
  - ✓ **Severe HIV disease**
  - ✓ **HIV disease progression**
  - ✓ **AIDS events**
  - ✓ **Non-AIDS events**
  - ✓ **Malignancy ( AIDS and non AIDS)**
  - ✓ **Tuberculosis**
  - ✓ **HIV transmission**
  - ✓ **SAE and lab abnormalities**
  - ✓ **Severe HIV disease or malignancy or mortality (combined outcome)**

WHEN TO START - 2015 RECOMMENDATIONS

# When to Start in Adults: Evidence Summary

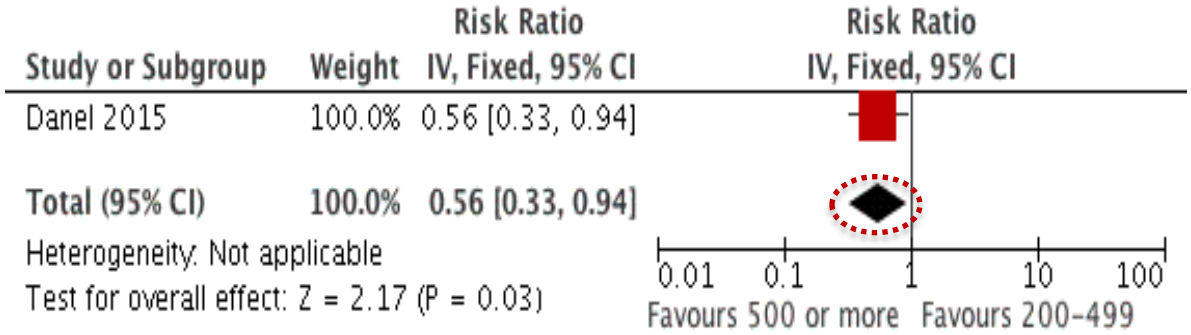
**A systematic review comparing ART initiation at CD4 <500 CD4 vs ≥500 CD4 cells/µL**

**1 RCT* (TEMPRANO) and 17 cohorts or meta-analyses of cohorts reporting on 8 separate outcomes**

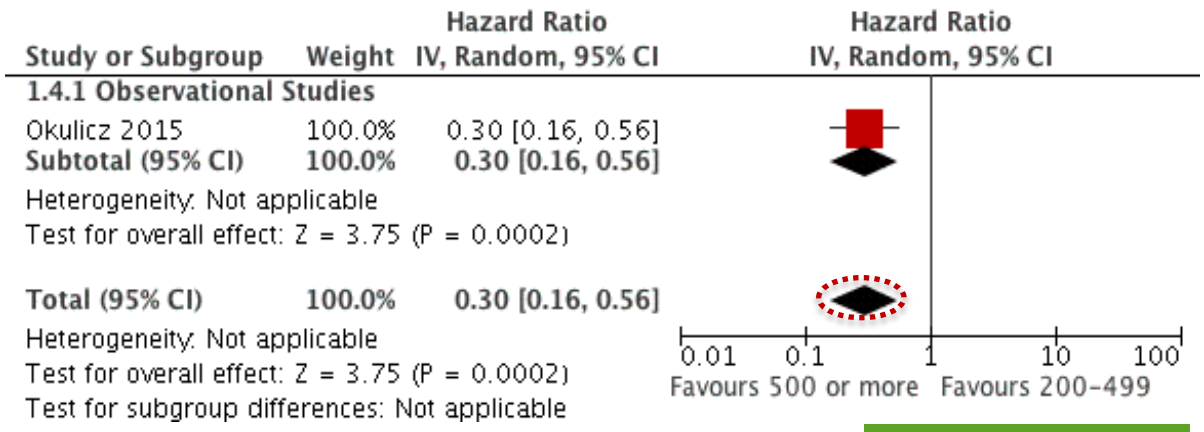
**Less severe HIV morbidity, HIV disease progression and HIV transmission, without increase in grade III/IV lab adverse events.**

*** Interim results of START study were also reviewed by GDG as a complementary assessment**

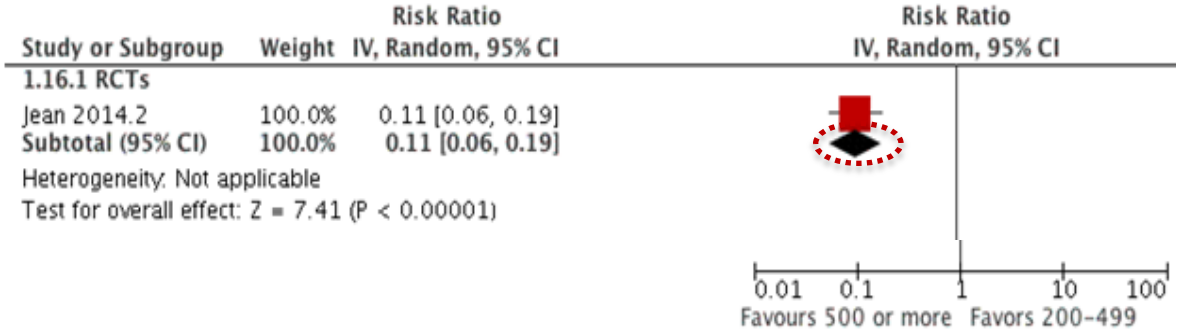
## Severe HIV morbidity



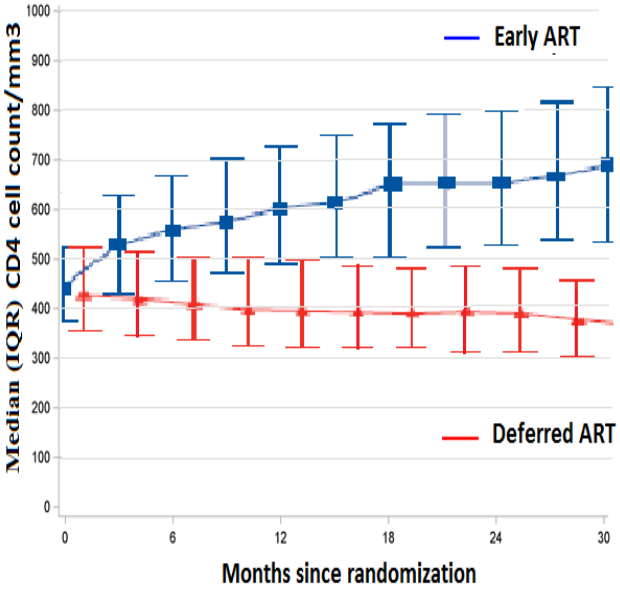

## HIV disease progression

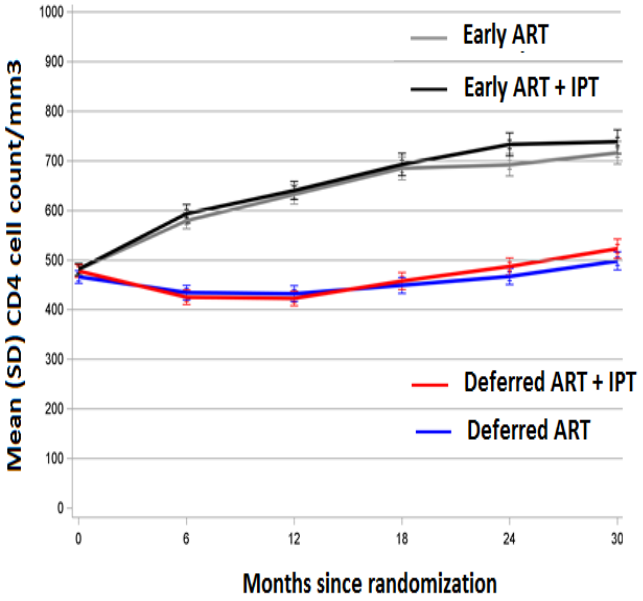


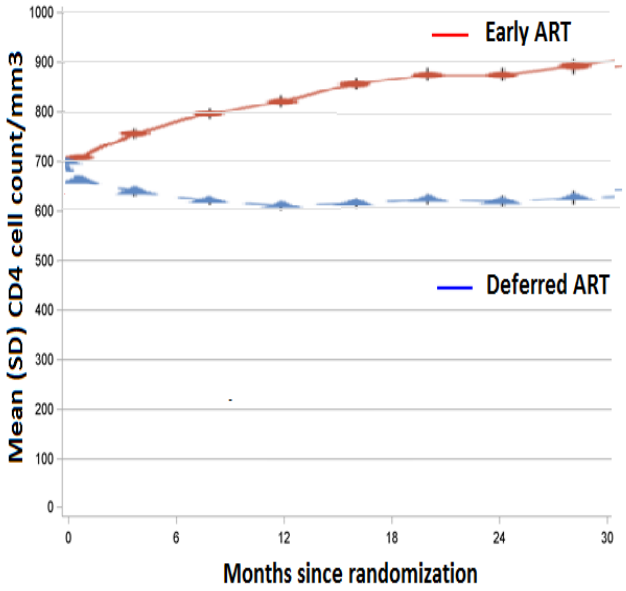

## HIV Transmission



# CD4 Inclusion Criteria




## HPTN052

- Inclusion : 350-550
- Initiate ARV: < 250

## TEMPRANO

- Inclusion : 250-800
- Initiate ARV: < 250
  < 350
  < 500

## START

- Inclusion : >500
- Initate ARV: < 350

*Angalret ANRS Sept 2015*

# Hazard ratio of primary outcome by study

| | Early treatment (n=886) | Delayed treatment (n=875) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| Any serious clinical event | 57 (6%) | 77 (9%) | 0·73 (0·52–1·03) | 0·074 |
| Any AIDS event | 40 (5%) | 61 (7%) | 0·64 (0·43–0·96) | 0·031 |
| Tuberculosis | 17 (2%) | 34 (4%) | 0·49 (0·28–0·89) | 0·018 |
| Severe bacterial infection* | 20 (2%) | 13 (1%) | .. | .. |
| Any WHO stage 4 event (excluding tuberculosis) | 9 (1%) | 19 (2%) | .. | .. |
| Non-AIDS event | 12 (1%) | 9 (1%) | 1·35 (0·57–3·19)‡ | 0·50 |
| All deaths | 11 (1%) | 15 (2%) | 0·73 (0·34–1·59)‡ | 0·43 |

| | Early ART | | | Deferred ART | | | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| | *no. of patients* | *person-yr* | *rate* | *no. of patients* | *person-yr* | *rate* | |
| Death or severe HIV-related illness (primary outcome) | 64 | 2313 | 2.8 | 111 | 2248 | 4.9 | 0.56 (0.41–0.76) |
| Death | 21 | 2520 | 0.8 | 26 | 2502 | 1.0 | 0.80 (0.45–1.40) |
| Death or AIDS | 50 | 2333 | 2.1 | 84 | 2288 | 3.7 | 0.58 (0.41–0.83) |
| AIDS | 33 | 2333 | 1.4 | 65 | 2288 | 2.8 | 0.50 (0.33–0.76) |
| Tuberculosis | 28 | 2337 | 1.2 | 55 | 2298 | 2.4 | 0.50 (0.32–0.79) |
| Invasive bacterial diseases | 14 | 2358 | 0.6 | 36 | 2332 | 1.5 | 0.39 (0.21–0.71) |

| | Immediate-Initiation | | Deferred-Initiation | | Hazard Ratio |
|---|---|---|---|---|---|
| | *no.* | *no./100 person-yr* | *no.* | *no./100 person-yr* | |
| Composite primary end point | 42 | 0.60 | 96 | 1.38 | 0.43 (0.30–0.62) |
| Serious AIDS-related event | 14 | 0.20 | 50 | 0.72 | 0.28 (0.15–0.50) |
| Serious non–AIDS | 29 | 0.42 | 47 | 0.67 | 0.61 (0.38–0.97) |
| Death from any cause | 12 | 0.17 | 21 | 0.30 | 0.58 (0.28–1.17) |
| Tuberculosis | 6 | 0.09 | 20 | 0.28 | 0.29 (0.12–0.73) |
| Kaposi's sarcoma | 1 | 0.01 | 11 | 0.16 | 0.09 (0.01–0.71) |
| Malignant lymphoma | 3 | 0.04 | 10 | 0.14 | 0.30 (0.08–1.10) |
| Cancer not related to AIDS | 9 | 0.13 | 18 | 0.26 | 0.50 (0.22–1.11) |
| Cardiovascular disease | 12 | 0.17 | 14 | 0.20 | 0.84 (0.39–1.81) |

**Hazard Ratio pour le critère de jugement principal**

## HPTN052

- 0.73 (0.52-1.03)

## TEMPRANO

- 0.56 (0.41-0.76)

## START

- 0.43 (0.30-0.62)

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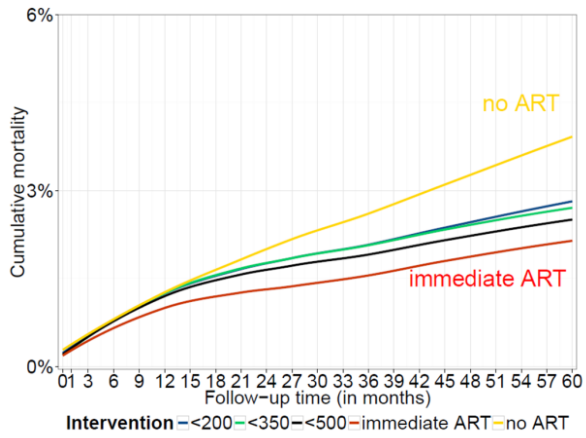
# Evidence for Children & Adolescents

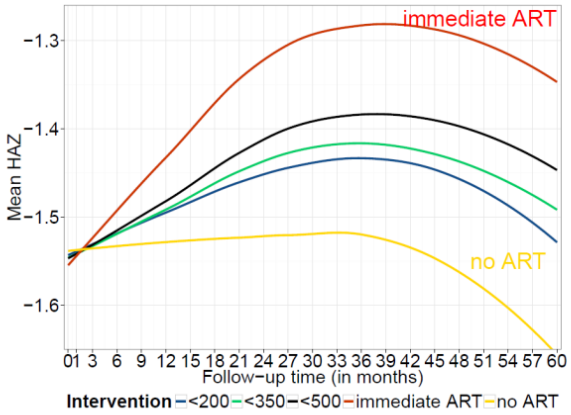
- **Lack of direct evidence** in support of earlier initiation (particularly for horizontally infected adolescents)[1]
- Indirect evidence suggests **reduction in mortality and improvement in growth** (particularly in children 5-10 years with CD4 >500)[2]
- A growing body of evidence demonstrates the **positive impactof ART** on growth[3], neurodevelopment[4], immunological recovery[5] and in preventing pubertal delays[6]
- Gains appear to be limited for vertically infected **adolescents**[2,5]

Mortality – age 5-10 – present with CD4> 500




Difference 'immediate ART' to '< 500':
0.4% (0.02%; 0.6%)

Growth - age 5-10 – present with CD4> 500




Difference 'immediate ART' to '< 500':
0.10 (0.07; 0.12)

*References:*
*1. Sigfried et al 2014*
*2. IeDea network 2015*
*3. McGrath et al 2011*
*4. Laughton et al 2012*
*5. Picat et al 2013*
*6. Szubert et al 2015*

# Community – led Global Consultation:

AFROCAB ICW VIA LIBRE Pangaea APN PLUS POSITIVE CHANGE EATG European AIDS Treatment Group AHF UKRAINE

## Acceptability of Earlier Initiation of ART

- 24 workshops, 8 countries, 8 sub populations, 206 people living with HIV, 74 service providers.
- Earlier initiation was deemed **acceptable**, specific considerations were highlighted
- **Collaborative decision-making** with the ultimate decision to initiate ART being client-driven
- The requirement for **comprehensive and accurate information** to ensure an informed decision as well as readiness
- Initiating ART is relatively easy however **maintaining adherence is challenging**
- **Stigma and discrimination** were uniformly raised as fundamental concerns by all and seen to constrain treatment access and adherence

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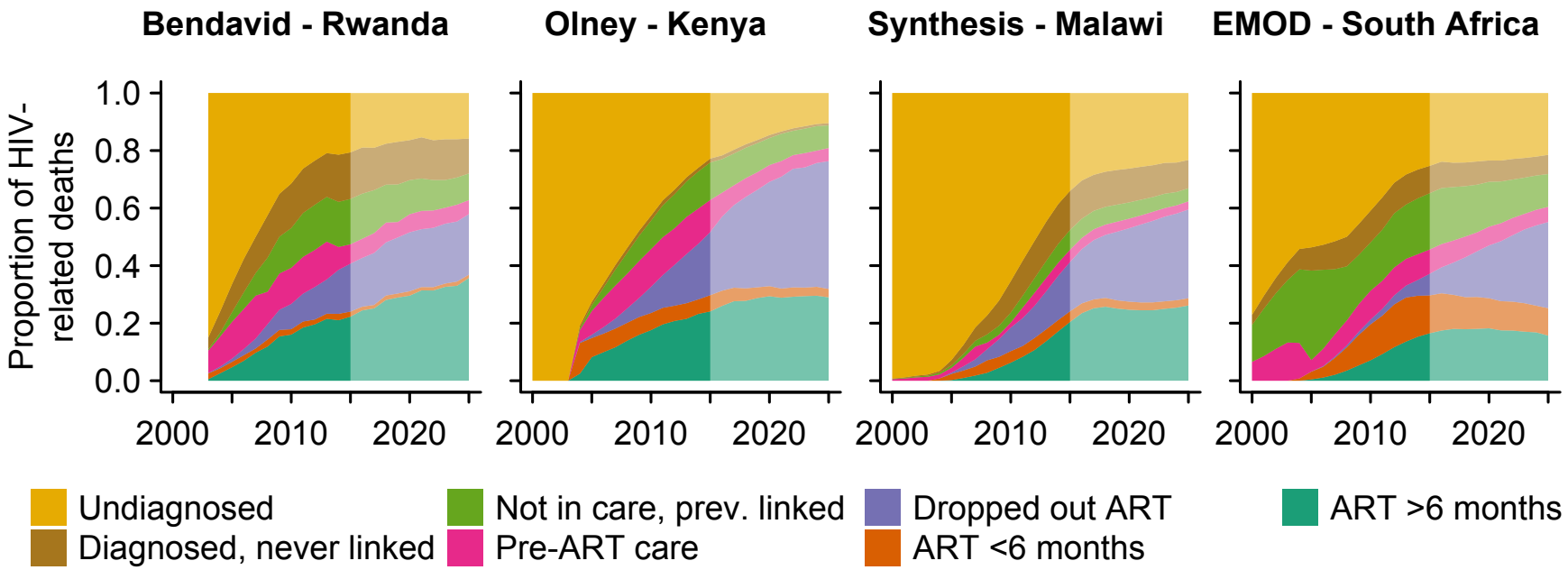
# Model Estimates and Projections






- More HIV-related deaths are among people on ART, but projections indicate that there will still be **25-40% of HIV deaths** among persons never initiated ART.
- Deaths among persons **disengaged from ART** care will **increase** to be a substantial proportion of HIV deaths (purple).
- Only **10-30%** of HIV deaths will be among adults stable on ART.

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# Why consider PrEP

**2.1 million people infected with HIV in 2013**

**Among key populations:**

- Burden of HIV infection is 19 fold higher among MSM and 49 fold higher among transgender women compared with the general population.
- High rates of HIV incidence among MSM across all regions.
- High HIV prevalence among sex workers in Africa >20% in Nigeria;>50% in South Africa and Zimbabwe.
- Estimates from South Africa show a 5.6% HIV prevalence among girls aged 15–19 years, increasing to 17.4% for young women aged 20–24 years.

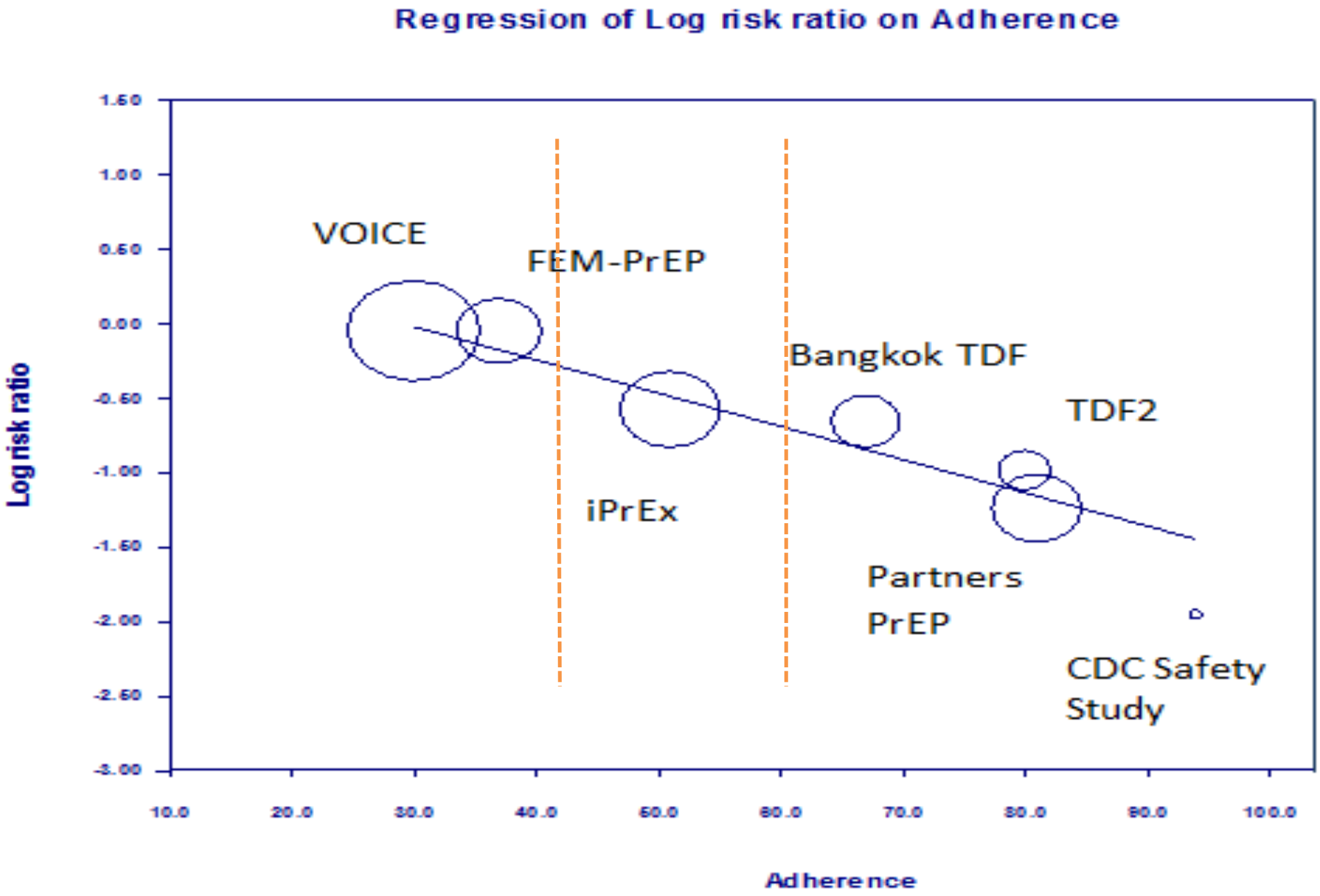
**Demonstrated need for more prevention options**

# PrEP Systematic review results

| Analysis | No. of studies | Sample Size (N) | Risk Ratio (95% CI) | p-value | $I^2$ | P-value (meta-regression) |
|---|---|---|---|---|---|---|
| **RCTs comparing PrEP to placebo** | | | | | | |
| **Overall** | 10 | 17424 | 0.49 (0.33-0.73) | 0.001 | 70.9 | -- |
| **Adherence** | | | | | | |
| **High (>70%)** | 3 | 6150 | 0.30 (0.21-0.45) | <0.0001 | 0.0 | <0.0001 |
| **Moderate (41-70%)** | 2 | 4912 | 0.55 (0.39-0.76) | <0.0001 | 0.0 | 0.009 |
| **Low (≤40%)** | 2 | 5033 | 0.95 (0.74-1.23) | 0.70 | 0.0 | *ref* |
| **Mode of Acquisition** | | | | | | |
| **Rectal** | 4 | 3167 | 0.34 (0.15-0.80) | 0.01 | 29.1 | 0.36 |
| **Vaginal/penile** | 6 | 14252 | 0.54 (0.32-0.90) | 0.02 | 80.1 | |
| **Biological sex[1]** | | | | | | |
| **Male** | 7 | 8706 | 0.38 (0.25-0.60) | <0.0001 | 34.5 | 0.19 |
| **Female** | 6 | 8716 | 0.57 (0.34-0.94) | 0.03 | 68.3 | |
| **Age[2]** | | | | | | |
| **18 to 24 years** | 3 | 2997 | 0.71 (0.47-1.06) | 0.09 | 20.5 | 0.29 |
| **≥25 years** | 3 | 5129 | 0.45 (0.22-0.91) | 0.03 | 72.4 | |
| **Drug Regimen** | | | | | | |
| **TDF** | 5 | 4303 active | 0.49 (0.28-0.86) | 0.001 | 63.9 | 0.88 |
| **FTC/TDF** | 7 | 5693 active | 0.51 (0.31-0.83) | 0.007 | 77.2 | |
| **Drug Dosing** | | | | | | |
| **Daily** | 8 | 17024 | 0.54 (0.36-0.81) | 0.003 | 73.6 | 0.14 |
| **Intermittent** | 1 | 400 | 0.14 (0.03-0.63) | 0.01 | 0.0 | |
| **RCTs comparing PrEP to no PrEP** | | | | | | |
| **Overall** | 2 | 720 | 0.15 (0.05-0.46) | 0.001 | 0.0 | NA |

[1] The iPrEx trial included 313 (13%) transgender women. [2] Includes only studies that stratified age by <25 and ≥25.

# PrEP Adherence and effectiveness



# WHO guidance on PrEP
## *(2012, 2014, 2015, 2016)*




**2012. Guidance for MSM & Serodiscordant Couples in the context of demonstration projects** *to encourage countries to conduct such demonstration projects*

**201. Consolidated KP Guidelines**

*Recommendation for MSM*

Among men who have sex with men, PrEP is recommended as **an additional HIV prevention choice** within a **comprehensive HIV prevention package** *(strong recommendation, high quality of evidence).*

**2015**

**Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches (Strong/High Quality)**

**2016**

**Implementation guidance, package of implementation tools for a variety of implementers and populations forthcoming**

**Implementation tool / guidance, *forthcoming***

# Who might benefit from PrEP – people at



**Step 1**. consider an incidence in a community/population of ≈ 3 per 100 person–years

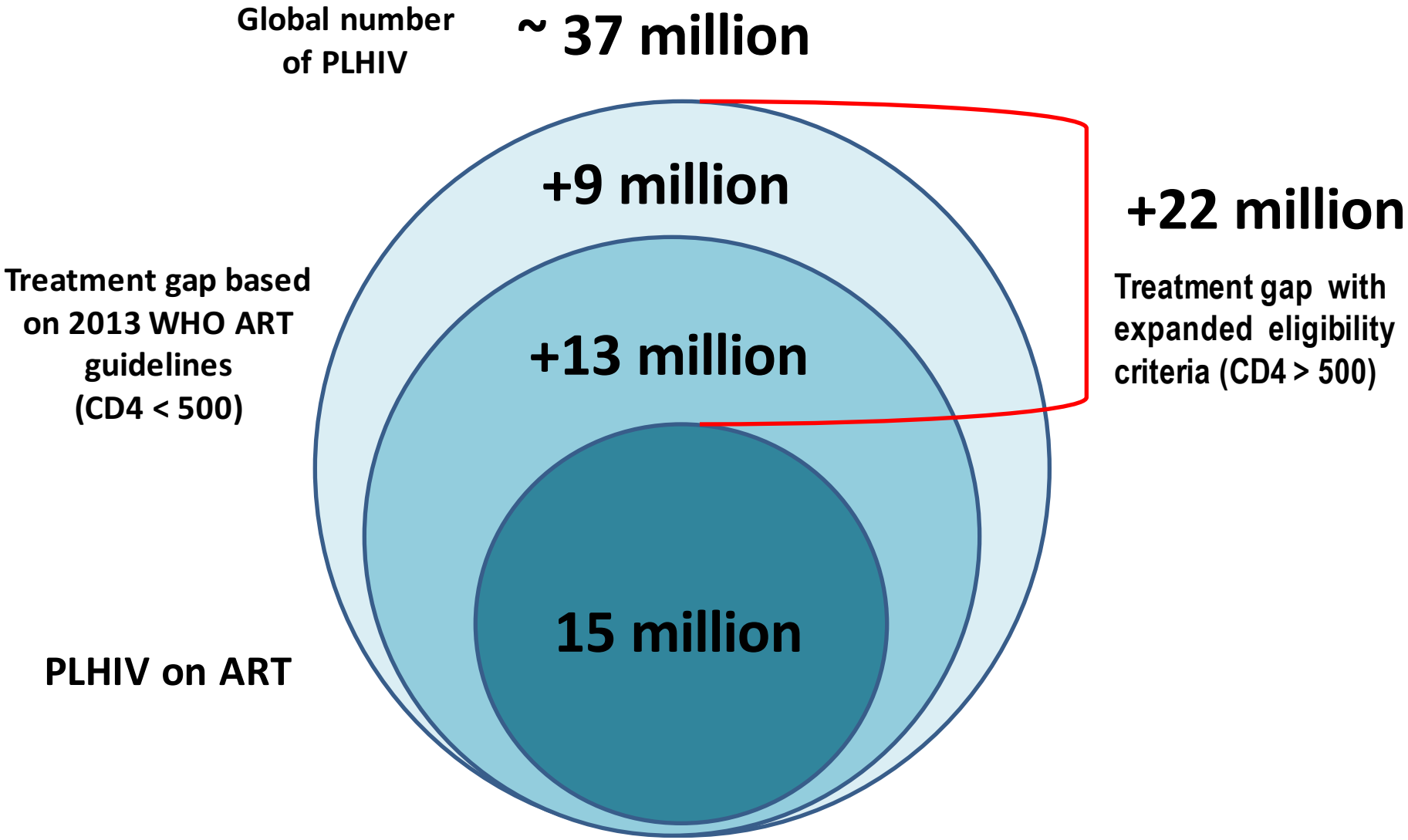
**Step 2.** Within a population with incidence ≈ 3% there will be significant heterogeneity. Not all people will have high HIV risk. Simple screening questions will help identify those at most risk within this population or community and those who are ***not*** using other effective HIV prevention methods

**Step 3 .**Those who are identified at highest HIV risk and a would welcome and want to take an additional prevention option

**'offering PrEP' could be considered.**

RESOURCE USE - COSTS

# The estimated gap between aspiration treatment targets & actual numbers of PLHIV on ART according to eligibility criteria




Concerns from countries/donors on how to address immediate increased cost and service demand

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# MDG results & new targets…



| Key parameters | 2005 | 2015 | 2020 | 2030 |
|---|---|---|---|---|
| New HIV infections | 3 million | 2 million [↓ 35%] | 500,000 | 200,000 |
| AIDS-associated deaths | 2.4 million | 1.2 million [↓ 50%] | 400,000 | 200,000 |
| PLHIV accessing ART | 1.5 million | 15 million [↑ 10x] | 30 million | ALL |
| Investments for global HIV response (US$) | 7 billion | 20 billion [↑ 3x] | 32 billion | 29 billion |

WHO & UNAIDS reports , 2015

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# What is new in the Early release guideline?

- Treat all (at any CD4) - people living with HIV across all ages
- The sickest remain a priority (symptomatic disease and CD4< 350)
- New age band for Adolescents (age 10-19)
- Option B not taken forward; Option B+ as the new standard
- PrEP recommended as an additional prevention choice for all people at substantial risk of HIV infection (> 3% incidence)

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# 2015 ARV : Timeline

HIV/AIDS Department

**Evidence retrieval:**
Systematic reviews
Values and preferences
Community consultations
Modelling
**Dec 2014 – May 2015**

**Key recommendations preview**
**July 19 2015**

**Launch Full Updated 2015 Consolidated ARV Guidelines**
**Dec 1 2015**

**Core group**
**July 23-24 2015**

**Supplement launch WAD**
**Dec 1 2014**

**GDG Clinical/ Operational**
**June 1-5 2015**
**June 16-19 2015**

**Launch Interim Guidelines on when to start and pre-exposure prophylaxis**
**Sept -Oct 2015**

**Core group**
**Oct 20-21 2014**

Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan

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**Michel Sidibé, Executive Director, UNAIDS**

"Everybody living with HIV has the right to life-saving treatment. The new guidelines are a very important step towards ensuring that all people living with HIV have immediate access to antiretroviral treatment."

**Deborah L. Birx, U.S. Global AIDS Coordinator & U.S. Special Representative for Global Health Diplomacy**

"PEPFAR applauds the World Health Organization on the release of their 'Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.'.. These are transformative to epidemic control. Short of an HIV vaccine or cure, this gives us the critical tools we need to create an AIDS-free generation utilizing the FAST TRACK strategy. We have no excuses - it is up to us to seize this moment…"

**Mark Dybul, Executive Director, The Global Fund**

"The two recommendations are critically important to moving us towards the fast-track treatment and prevention goals…. We must embrace ambition if we are going to end HIV as a public health threat."

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