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

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2 Oct 2015
IAPAC Summit, Paris
Acknowledgements

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. Thank you to IAPAC for opportunity to share these guidelines.

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The Global Network of People living with HIV/AIDS
PEPFAR
CDC
USAID
Bill and Melinda Gates Foundation
Progress in access to antiretroviral therapy: 2000–2015

The last decade of scale up:
- Price reductions
- Major investments
- New service models

ART coverage

“15 BY 15”
A GLOBAL TARGET ACHIEVED
Uptake of WHO policy for initiation threshold among adults and adolescents living with HIV in low- and middle-income countries (situation as of end 2014)

Policies adopted in 144 LMIC
6% - treat all
53% - CD4 ≤ 500
Implementation and practice of initiating ART at a CD4 threshold of 500 among adults and adolescents living with HIV in low- and middle income countries (situation as of end 2014)

Implementation CD4 < 500 in 104 LMIC
52% - country wide implementation

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
WHO 2013 Consolidated ARV Guidelines
Policy uptake in 58 WHO focus Countries End 2014
(% responding yes, by region)

Policy uptake in 58 WHO focus Countries End 2014
(% responding yes, by region)
% Uptake of Service Delivery Integration Policies in the 58 WHO focus countries, end 2014

- ART provision in TB clinics
- TB treatment in ART settings
- ART provision in MNCH clinics
- ART provision in OST settings
- Community health workers engaged in ART patient support

% Policies for Adults
% Policies for Children
2015 WHO Consolidated ARV Guidelines

**Clinical**
- How to do it well?
  - Care Packages (Differentiated/Adaptive Care)
  - Linkages, Retention, Adherence
  - Quality of care
  - Diagnostics
  - Supply chain

**Programmatic Prioritization**
- How to decide?
  - Approaches to prioritization & sequencing
  - Tool kits for country adaptation and implementation

**Operational & Service Delivery**
- 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

HIV Treatment

**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

**HOW TO DECIDE?**
- Approaches to prioritization & sequencing
- Tool kits for country adaptation and implementation
ART eligibility: 5 policy scenarios

Estimated millions of people eligible for ART (2014)

1. CD4 ≤ 200
   Recommended since 2003

2. CD4 ≤ 350
   Recommended since 2010

3. CD4 ≤ 350 + TasP
   Incremental approach 2012

4. CD4 ≤ 500
   + indications for ART at any CD4
   2013 guidelines

5. All HIV+
   Treat ALL
   2015 guidelines

30 m. 36.9 m.
<table>
<thead>
<tr>
<th>Target Population</th>
<th>Specific Recommendation</th>
<th>Recommendation Strength</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>ART initiation at any CD4</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ART initiation if WHO clinical stage III/IV or CD4 ≤ 350 as priority</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnant/BF women</td>
<td>ARV initiation at any CD4 and continued lifelong (Option B+)</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adolescents</td>
<td>ART initiation if 10-19 years-old</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>ART initiation if WHO clinical stage III/IV or CD4 ≤ 350 as priority</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Children</td>
<td>ART initiation if 1-10 years-old</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>ART initiation if &lt; 1 year-old</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ART initiation if &lt; 2 years-old or WHO clinical stage III/IV or CD4 &lt; 25% (&lt; 5 years) or ≤ 350 (&gt;5 years) as priority</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
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)**
**Evidence Summary: Risk of death, severe HIV disease or HIV disease progression**

**Clinical trials**
Moderate quality evidence for lower risk of death, severe HIV disease or malignancy compared to those deferring treatment (1 study)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danel 2015</td>
<td>100.0%</td>
<td>0.56 [0.33, 0.94]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.56 [0.33, 0.94]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)

**Observational studies**
Very low quality evidence for lower risk of death or progression to AIDS compared to those deferring treatment (2 studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.2 Observational Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASCADE 2011</td>
<td>61.0%</td>
<td>1.10 [0.67, 1.79]</td>
</tr>
<tr>
<td>Garcia 2004</td>
<td>39.0%</td>
<td>0.26 [0.06, 1.07]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.63 [0.16, 2.49]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.75; Chi^2 = 3.56, df = 1 (P = 0.05); I^2 = 72%
Test for overall effect: Z = 0.66 (P = 0.51)

CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial
Severe HIV morbidity on TEMPRANO & START studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Danel 2015</td>
<td>31.8%</td>
<td>0.59 [0.34, 1.01]</td>
<td></td>
</tr>
<tr>
<td>START 2015</td>
<td>68.2%</td>
<td>0.49 [0.34, 0.71]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.52 [0.38, 0.70]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \chi^2 = 0.31, \text{df} = 1 (P = 0.58); I^2 = 0\%

Test for overall effect: \( z = 4.22 (P < 0.0001) \)

CI confidence interval; IV, inverse variance; RCT, randomised controlled trial
Evidence Summary: Risk of Hepatic and Renal SAE

**Clinical trial**
Low quality evidence for no increased risk of hepatic and renal SAE between early vs deferred treatment (1 study)

**Observational studies**
Low quality evidence for increased risk of hepatic SAE compared to those deferring treatment but no increased risk for renal SAE (1 study)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.13.1 RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniel 2015</td>
<td>100.0%</td>
<td>0.76 [0.20, 2.85]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.76 [0.20, 2.85]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.40 (P = 0.69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jose 2014 (1)</td>
<td>100.0%</td>
<td>1.45 [1.03, 2.04]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>1.45 [1.03, 2.04]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.15 (P = 0.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.14.1 RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniel 2015</td>
<td>100.0%</td>
<td>0.09 [0.01, 1.54]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.09 [0.01, 1.54]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.66 (P = 0.10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jose 2014</td>
<td>100.0%</td>
<td>0.90 [0.40, 2.01]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.90 [0.40, 2.01]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.26 (P = 0.80)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When to Start in Adults: Evidence Summary

- Evidence show clinical benefits of ART initiation over 500 CD4 to all PLHIV compared with < 500 CD4 initiation, with reduction of severe HIV morbidity, HIV disease progression and HIV transmission, without increase in grade III/IV adverse events.
  - Quality of evidence for the combined outcome of death, severe HIV disease or malignancy was of moderate quality
  - Quality of evidence for any Grade 3 or 4 laboratory abnormalities was also of moderate quality
  - Quality evidence for HIV disease progression and HIV transmission was very low
  - All other outcomes showed evidence of low to very low quality, including mortality, incident malignancies, tuberculosis, non-AIDS events, and specific SAEs
Number of participants and location

HPTN052
- Total: 1761
  - Africa 54%


Temprano: Temprano study group, *NEJM* 2015; 373:808-22

START: INSIGHT START study group, *NEJM* 2015; 373:795-807

START
- Total: 4651
  - Africa 21%
CD4 Inclusion Criteria

**HPTN052**
- Inclusion: 350-550
- Initiate ARV: < 250

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

**START**
- Inclusion: >500
- Initiate ARV: < 350

Angalret ANRS Sept 2015
Primary outcomes

HPTN052
- Death
- WHO Stage 4
- Tuberculosis
- Cancers non-AIDS
- Severe bacterial infections
- CVD
- Diabetes

TEMPRANO
- Death
- WHO Stage 4
- Tuberculosis
- Cancers non-AIDS
- Severe bacterial infections

START
- Death
- AIDS (except oral candida and invasive HSV)
- Tuberculosis
- Cancers non-AIDS
- CVD
- Renal insufficiency
- Severe hepatic insufficiency

Angalret ANRS Sept 2015
Hazard ratio of primary outcome by study

HPTN052  •  0.73 (0.52-1.03)

TEMPRANO  •  0.56 (0.41-0.76)

START  •  0.43 (0.30-0.62)
When to Start
Children and Adolescents

- ART should be initiated in all adolescents with HIV regardless of WHO clinical stage and at any CD4 cell count (*conditional recommendation, low-quality evidence*).

- ART should be initiated in all children infected with HIV, regardless of WHO clinical stage or CD4 cell count
  - Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
  - Children infected with HIV one year to less than 10 years of age (*conditional recommendation, low-quality evidence*).

<table>
<thead>
<tr>
<th>Age</th>
<th>When you start</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years to less than 19 years</td>
<td>Treat all adolescents Individuals with WHO clinical stage 3 or 4 and with CD4 count ≤ 350 cells/mm³ as a priority</td>
</tr>
<tr>
<td>1 year to less than 10 years</td>
<td>Treat all children (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or &lt;25% in younger than 5 years and CD4 count ≤350 cells/mm³ in 5 years and older as a priority)</td>
</tr>
<tr>
<td>Infants (&lt;1 year)</td>
<td>Treat all infants</td>
</tr>
</tbody>
</table>
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 impact of ART** on growth\(^3\), neurodevelopment\(^4\), immunological recovery\(^5\) and in preventing pubertal delays\(^6\)

- Gains appear to be limited for vertically infected **adolescents**\(^2,5\)

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
Programmatic Rationale
Children and Adolescents

Only ~20% are not eligible based on existing criteria

- **Eliminates the need** for determining CD4 count to initiate ART
- **Avoids delaying** ART in settings without access to CD4 testing.
- **Simplifies** paediatric treatment and facilitate expansion of paediatric ART (task-shifting and decentralization)
- **Improves** retention in care compared to pre-ART

However...need adherence support (particularly in adolescents), careful planning, strengthening laboratory services and improvement of procurements and supply of key commodities

*Source: Uganda National programme - Rapid assessment May 2015*
Community – led Global Consultation:

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
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.

*Source: HIV Modeling Consortium June 2015*
Countries are leading the way

Examples from five countries implementing Treat All or Treating All in specific populations:

- **Brazil** has been treating all for one year
- Leading to increase in median CD4 at ART initiation (265 to 419)
- Similar retention and VLS at 12 months (81% for CD4 > 500)

- **Uganda** started to treat all children < 15 years in 2014
- Seen increase in overall number children on ART
- Retention at 12 m similar; VLS = 84%
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
### HIV in pregnant women in rural South Africa (2001-2013)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=4818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>11.5%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>30.4%</td>
</tr>
<tr>
<td>21-22</td>
<td>39.4%</td>
</tr>
<tr>
<td>23-24</td>
<td>49.5%</td>
</tr>
<tr>
<td>&gt;25</td>
<td>51.9%</td>
</tr>
</tbody>
</table>

**Source**: Abdool Karim Q, Int J Epi, 2014

---

HIV incidence in 18-35 year women in this community: **9.1%**

9.1 per 100 women-yrs (95% CI: 7 - 12)

**Source**: Abdool Karim Q et al, Science 2010
## PrEP Systematic review results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>Sample Size (N)</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
<th>I²</th>
<th>P-value (meta-regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCTs comparing PrEP to placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>17424</td>
<td>0.49 (0.33-0.73)</td>
<td>0.001</td>
<td>70.9</td>
<td>--</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;70%)</td>
<td>3</td>
<td>6150 4912 5033</td>
<td>0.30 (0.21-0.45)</td>
<td>&lt;0.0001</td>
<td>0.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate (41-70%)</td>
<td>2</td>
<td>4912 5033</td>
<td>0.55 (0.39-0.76)</td>
<td>&lt;0.0001</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Low (≤40%)</td>
<td>2</td>
<td>4912 5033</td>
<td>0.95 (0.74-1.23)</td>
<td>0.70</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Mode of Acquisition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>4</td>
<td>3167 14252</td>
<td>0.34 (0.15-0.80)</td>
<td>0.01</td>
<td>29.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Vaginal/penile</td>
<td>6</td>
<td>14252</td>
<td>0.54 (0.32-0.90)</td>
<td>0.02</td>
<td>80.1</td>
<td></td>
</tr>
<tr>
<td><strong>Biological sex¹</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>8706 8716</td>
<td>0.38 (0.25-0.60)</td>
<td>&lt;0.0001</td>
<td>34.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>8716</td>
<td>0.57 (0.34-0.94)</td>
<td>0.03</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td><strong>Age²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 24 years ≤25 years</td>
<td>3</td>
<td>2997 5129</td>
<td>0.71 (0.47-1.06)</td>
<td>0.09</td>
<td>20.5</td>
<td>0.29</td>
</tr>
<tr>
<td>≥25 years</td>
<td>3</td>
<td>5129</td>
<td>0.45 (0.22-0.91)</td>
<td>0.03</td>
<td>72.4</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>5</td>
<td>4303 active</td>
<td>0.49 (0.28-0.86)</td>
<td>0.001</td>
<td>63.9</td>
<td>0.88</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>7</td>
<td>5693 active</td>
<td>0.51 (0.31-0.83)</td>
<td>0.007</td>
<td>77.2</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Dosing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>8</td>
<td>17024 400</td>
<td>0.54 (0.36-0.81)</td>
<td>0.003</td>
<td>73.6</td>
<td>0.14</td>
</tr>
<tr>
<td>Intermittent</td>
<td>1</td>
<td>400</td>
<td>0.14 (0.03-0.63)</td>
<td>0.01</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td><strong>RCTs comparing PrEP to no PrEP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2</td>
<td>720</td>
<td>0.15 (0.05-0.46)</td>
<td>0.001</td>
<td>0.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

Regression of Log risk ratio on Adherence

- VOICE
- FEM-PrEP
- Bangkok TDF
- TDF2
- Partners
- PrEP
- CDC Safety Study
## GRADE table: HIV infection

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Oral PrEP (containing tenofovir)</th>
<th>Control</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Infection—PrEP vs. Placebo—Adherence &gt;70%</strong></td>
<td>3</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>39/3866 (1%)</td>
<td>79/2284 (3.5%)</td>
<td>RR 0.30 (0.21 to 0.45)</td>
<td>24 fewer per 1000 (from 19 fewer to 27 fewer)</td>
<td>⬤⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td><strong>HIV Infection—PrEP vs. Placebo—Adherence 40-70%</strong></td>
<td>2</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>53/2455 (2.2%)</td>
<td>97/2457 (3.9%)</td>
<td>RR 0.55 (0.39 to 0.76)</td>
<td>18 fewer per 1000 (from 9 fewer to 24 fewer)</td>
<td>⬤⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td><strong>HIV Infection—PrEP vs. Placebo—Adherence &lt;40%</strong></td>
<td>2</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>146/3002 (4.9%)</td>
<td>95/2031 (4.7%)</td>
<td>RR 0.95 (0.74 to 1.23)</td>
<td>2 fewer per 1000 (from 12 fewer to 11 more)</td>
<td>⬤⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td><strong>HIV infection—PrEP vs. no PrEP</strong></td>
<td>2</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>3/367 (0.82%)</td>
<td>22/353 (6.2%)</td>
<td>RR 0.15 (0.05 to 0.46)</td>
<td>53 fewer per 1000 (from 34 fewer to 59 fewer)</td>
<td>⬤⬤⬤⬤ HIGH</td>
</tr>
</tbody>
</table>
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 'substantial' HIV risk

Step 1. consider an incidence in a community/population of \( \approx 3 \) per 100 person-years

Step 2. Within a population with incidence \( \approx 3\% \) 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
Global estimates (2014-2015) vs the gap to reach 90-90-90 targets in 2020

- **HIV Positive People**: 36.9 million
- **Diagnosed**: 19.8 million
  - **Breakpoint 1**: 13.4 million Undiagnosed (53%)
  - **Breakpoint 2**: 14.9 million not treated (41%)
  - **Breakpoint 3**: 15.3 million not virally suppressed (32%)
  - **Viral Suppression <1000 (ITT)**: 11.6 million

Critical issues addressed in New HTS Guidelines

- **New approaches**
  - Trained lay providers testing (*new recommendation*)
  - Test for Triage (*new testing strategy*)
  - HIV self-testing (*push for implementation and monitoring*)

- **Better linkage**

- **Preventing misdiagnosis**
  - Focus on QA
  - Re-emphasise re-testing all +ve before ART initiation

- **Strategic choices**
Consolidated Strategic Information Guidance

HIV Treatment

Know your epidemic → Inputs → Outputs & Outcomes → Evaluate impact

Epidemic pattern by key population, age, sex and geography
Health system inputs and financing

Outputs & Outcomes
HIV care cascade

Prevention
Testing & counselling
Linkage to care
ART
Viral suppression

(1) People with HIV
   Number and % of people living with HIV (PLHIV)

(2) Domestic finance
   % of HIV response financed domestically

(3) Prevention by key populations
   % condom use among key populations or needles per PWID

(4) Knowing HIV status
   % of PLHIV who have been diagnosed

(5) Linkage to care
   Number and % in HIV care (including ART)

(6) Currently on ART
   % on ART

(7) ART retention
   % retained and surviving on ART

(8) Viral suppression
   % on ART virally suppressed

(9) HIV deaths
   Number and ratio of HIV-related deaths

(10) New infections
    Number and % of new HIV infections

10 Global Indicators
The estimated gap between treatment targets & actual numbers of PLHIV on ART according to eligibility criteria

Global number of PLHIV ~ 37 million

15 million

+9 million

+13 million

+22 million

Concerns from countries/donors on how to address immediate increased cost and service demand
From UNAIDS Fast Track Modeling

Resources and investment portfolio, 2013-2030

- **2013**: US$ 20.4 billion
  - Treatment: 49%
  - Prevention: 28%
  - Critical enablers: 16%
  - Synergies: 7%

- **2020**: US$ 31.9 billion
  - Treatment: 48%
  - Prevention: 23%
  - Critical enablers: 19%
  - Synergies: 7%

- **2030**: US$ 29.3 billion
  - Treatment: 45%
  - Prevention: 21%
  - Critical enablers: 21%
  - Synergies: 7%

## MDG results & new targets...

<table>
<thead>
<tr>
<th>Key parameters</th>
<th>2005</th>
<th>2015</th>
<th>2020</th>
<th>2030</th>
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<tbody>
<tr>
<td>New HIV infections</td>
<td>3 million</td>
<td>2 million</td>
<td>500,000</td>
<td>200,000</td>
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<td></td>
<td><img src="35" alt="35%" /></td>
<td><img src="50" alt="50%" /></td>
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<tr>
<td>AIDS-associated deaths</td>
<td>2.4 million</td>
<td>1.2 million</td>
<td>400,000</td>
<td>200,000</td>
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<tr>
<td></td>
<td><img src="50" alt="50%" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLHIV accessing ART</td>
<td>1.5 million</td>
<td>15 million</td>
<td>30 million</td>
<td>ALL</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Investments for global HIV response (US$)</td>
<td>7 billion</td>
<td>20 billion</td>
<td>32 billion</td>
<td>29 billion</td>
</tr>
<tr>
<td></td>
<td><img src="3x" alt="3x" /></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**WHO & UNAIDS reports, 2015**
Results: Programme Managers Survey

Figure 1: Country HIV epidemic settings of survey respondents (N=41)

- Generalised epidemic setting: 22%
- Generalised with specific geographies of high prevalence: 15%
- Low prevalence: 34%
- Concentrated epidemic: 29%

Source: National ART Programme managers perspectives’ on implementing HIV interventions, KIT 2015

Figure 2: Top 3 requirements to enable your country to expand ARV treatment initiation criteria for each of the groups stated (N=33)

- Adults:
  - Greater preparation of the health system: 23%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 22%
  - A greater desire from the community: 6%
  - More evidence on eligibility: 8%
  - More trained health care workers: 19%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 22%
- Children <15 years:
  - Greater preparation of the health system: 23%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 20%
  - A greater desire from the community: 11%
  - More evidence on eligibility: 6%
  - More trained health care workers: 24%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 15%
- Adolescents:
  - Greater preparation of the health system: 20%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 15%
  - A greater desire from the community: 12%
  - More evidence on eligibility: 5%
  - More trained health care workers: 24%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 22%
- Pregnant and breastfeeding women:
  - Greater preparation of the health system: 23%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 15%
  - A greater desire from the community: 13%
  - More evidence on eligibility: 4%
  - More trained health care workers: 28%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 17%
- Key populations:
  - Greater preparation of the health system: 22%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 11%
  - A greater desire from the community: 16%
  - More evidence on eligibility: 6%
  - More trained health care workers: 25%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 20%
- Positive person of s/d couples:
  - Greater preparation of the health system: 21%
  - Increased local country or MoH funds to expand treatment (health systems and purchasing ARVs): 12%
  - A greater desire from the community: 15%
  - More evidence on eligibility: 10%
  - More trained health care workers: 27%
  - Increased access to donor funds to expand treatment (health systems and purchasing ARVs): 14%
  - I don’t know: 1%
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

"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.”
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)
2015 ARV : Timeline

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

Supplement launch WAD
  Dec 1 2014

Core group
  Oct 20-21 2014

Key recommendations preview
  July 19 2015

Core group
  July 23-24 2015

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

Launch Full Updated 2015 Consolidated ARV Guidelines
  Dec 1 2015

Core group
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Acknowledgements

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. Thank you to IAPAC for opportunity to share these guidelines.

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IeDEA Collaboration
The Global Network of People living with HIV/AIDS
PEPFAR
CDC
USAID
Bill and Melinda Gates Foundation