New Directions in the 2015 Consolidated ARV Guidelines Update

Meg Doherty, MD, PhD, MPH
19 July 2015
WHO Satellite
Vancouver – IAS 2015
Objectives of Presentation

• 2015 ARV Guidelines update - why now?

• Overview of Evidence Base

• New directions in guidance
Why do we need 2015 ARV guidelines?

**New Science**
- Early treatment trials starting to report (TEMPRANO, START)
- Data on safety of key ARVs in specific populations

**New Commodities**
- New ARVs at new doses & formulations (INI, low dose EFV, DVR/r FDC)
- Treatment optimisation for children and adolescents (pellets, new strategies)

**New Technologies**
- Balance of POC versus standard CD4, VL and EID platforms

**Rethink Service Delivery Models**
- Preparation for greater numbers on ARV; improve linkage, referral, adherence approaches; Enhance efficiency and maintain quality
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
Clinical Programmatic Prioritization

HOW TO DO IT WELL?
- Care Packages (Differentiated/Adaptive Care)
- Linkages, Retention, Adherence
- Quality of care
- Diagnostics
- Supply chain

HOW TO DECIDE?
- Approaches to prioritization & sequencing
- Tool kits for country adaptation and implementation

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

Operational & Service Delivery

Programmatic Prioritization

WHO Consolidated ARV Guidelines
2015 ARV Guidelines Process

- **SYSTEMATIC REVIEWS**
- **GREY LITERATURE**
- **MODELLING (HIV MC, IeDEA)**
- **SURVEY OF ARV & LAB USE (AMDS, GARPr)**
- **DRUG COSTING (GPRM, AMDS)**

### Key Components

- **2013 RECOMMENDATIONS**
- **QUALITY OF EVIDENCE**
- **VALUES & PREFERENCES**
- **FEASIBILITY & COST**

### Inputs

- **QUALITATIVE DATA REVIEWS**
- **QUALITY (GNP+ FORUM)**
- **COMMUNITY & HCW CONSULTATIONS**
- **PROGRAMME MANAGERS SURVEY (KIT)**
Overview of when to start ART studies

1995-2005

Several ACTG and CPCRA studies (early Post HAART Era): ART initiation CD4 < 200 cells/mm$^3$ - Impact on AIDS mortality and major OIs incidence

2005-2010

CIPRA and SMART studies (ART initiation at CD4 ≤ 350 cells/mm$^3$) Impact on HIV mortality, dz progression, & co-morbidities (TB)

2010-2013

Observational studies (ART initiation at CD4 > 350 cells/mm$^3$) impact on mortality, dz progression & non-AIDS events

2015

TEMPRANO and START studies: (ART initiation at CD4 > 500 cells/mm$^3$) impact on severe HIV morbidity & disease progression, without increase in severe adverse events

HPTN 052: reduction of HIV transmission among HIV serodiscordant couples and risk of TB in adults (impact on HIV incidence)
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
<table>
<thead>
<tr>
<th>Target population</th>
<th>WHAT IS EXPECTED IN 2015 ART GUIDELINES?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>ART initiation at any CD4 NEW</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART initiation if WHO clinical stage III/IV or CD4 ≤ 350</td>
</tr>
<tr>
<td>Pregnant/BF women</td>
<td>ARV initiation at any CD4 and continued lifelong (Option B+) REVISED</td>
</tr>
<tr>
<td>Adolescents (10-19 year old)</td>
<td>ART initiation at any CD4 NEW</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART initiation if WHO clinical stage III/IV or CD4 ≤ 350</td>
</tr>
<tr>
<td>Children</td>
<td>ART initiation at any CD4 if 1-10 years-old NEW</td>
</tr>
<tr>
<td></td>
<td>ART initiation at any CD4 if &lt; 1 year-old</td>
</tr>
<tr>
<td></td>
<td>As a priority, 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)</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
- Evidence for lower risk of death, severe HIV disease or malignancy compared to those deferring treatment (1 study TEMPRANO)

<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><strong>Total (95% CI)</strong></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
- 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><strong>Subtotal (95% CI)</strong></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 ($P = 0.06$); $I^2 = 72$
- Test for overall effect: $Z = 0.66$ ($P = 0.51$

CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial
Evidence Summary: Risk of HIV transmission

**Clinical Trial (1 RCT)**
Evidence for lower risk of HIV transmission compared to those deferring treatment

**Observational studies**
Evidence for no significant difference in the risk of HIV transmission between early vs deferred treatment (2 studies)

### Clinical Trial (1 RCT)
- Evidence for lower risk of HIV transmission compared to those deferring treatment

### Observational studies
- Evidence for no significant difference in the risk of HIV transmission between early vs deferred treatment (2 studies)

#### Study or Subgroup | Weight | IV, Random, 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jean 2014.2</td>
<td>100.0%</td>
<td>0.11 [0.06, 0.19]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.11 [0.06, 0.19]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 7.41 (P < 0.00001)

#### Study or Subgroup | Weight | IV, Random, 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnell 2010</td>
<td>8.9%</td>
<td>3.82 [0.16, 88.40]</td>
</tr>
<tr>
<td>He 2013</td>
<td>91.1%</td>
<td>1.04 [0.39, 2.77]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>1.17 [0.46, 2.98]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

CI confidence interval; IV, inverse variance; RCT, randomised controlled trial
Evidence Summary: Risk of Hepatic & Renal SAE or any grade III/IV SAE

Clinical trial
no increased risk of hepatic and renal SAE between early vs deferred treatment (1 study)

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

Combined
No increased risk of any grade 3 / 4 SAE between early and deferring treatment (2 studies)
When to Start in Adults: Evidence Summary

- Systematic review on when to start ART in asymptomatic PLHIV found 1 RCT and 17 cohorts or meta-analyses of cohorts reporting on 8 separate outcomes in patients with <500 CD4 and ≥500 CD4 cells/µL.

- 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.
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. leDea 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

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

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.

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

2014
**Consolidated Key Populations 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

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**

- Not population specific
- **Significant HIV risk** means HIV incidence > 3 per 100 py
Overall evidence for PrEP: July 2015

**Study**

- **IPERGAY – on demand Truvada** (MSM – France & Canada)
  - Effect size (CI): 86% (39; 99)

- **PROUD – daily oral Truvada** (MSM – United Kingdom)
  - Effect size (CI): 86% (62; 96)

- **Partners PrEP – daily Truvada** (Discordant couples – Kenya, Uganda)
  - Effect size (CI): 75% (55; 87)

- **Partners PrEP – daily oral Tenofovir** (Discordant couples – Kenya, Uganda)
  - Effect size (CI): 67% (44; 81)

- **TDF2 – daily Truvada** (Heterosexuals men and women- Botswana)
  - Effect size (CI): 62% (22; 84)

- **iPrEx – daily Truvada** (MSM - America’s, Thailand, South Africa)
  - Effect size (CI): 44% (15; 63)

- **FEMPrEP – daily Truvada** (Women – Kenya, South Africa, Tanzania)
  - Effect size (CI): 6% (-52; 41)

- **MTN003/VOICE – daily Truvada** (Women – South Africa, Uganda, Zimbabwe)
  - Effect size (CI): -4% (-49; 27)

- **MTN003/VOICE – daily Viread** (Women - South Africa, Uganda, Zimbabwe)
  - Effect size (CI): -49% (-129; 3)

- **CAPRISA 004 – coital Tenofovir gel** (Women – South Africa)
  - Effect size (CI): 39% (6; 60)

- **MTN003/VOICE – daily Tenofovir gel** (Women – South Africa, Uganda, Zimbabwe)
  - Effect size (CI): 15% (-21; 40)

- **FACTS 001– coital Tenofovir gel** (Women – South Africa)
  - Effect size (CI): 0% (-40, 30)
What to use in first line ARV Therapy

- systematic review using a comparative pairwise and network meta-analysis evaluated 76 trials for direct and indirect evidence
  - 35,270 patients randomized to 171 treatment arms
- Direct evidence for comparative efficacy and safety of INSTIs compared to EFV was obtained from 6 RCTs
  - SINGLE, PROTOCOL 004, GS 102 study, GS 104 study, SPRING-1 and STARTMRK.
- The evidence on low dose EFV (EFV 400) came from ENCORE 1.

Edward Mills, Steve Kanters, M. Eugenia Socias, For WHO ARV GDG, June 1-5 2015
Directions of the Systematic Review

- All treatment regimens are comparable with respect to mortality or AIDS defining illnesses.

- Evidence that DTG and EFV400 superior with respect CD4 recovery at 24, 48 and 96 weeks

- INSTIs (DTG > RAL) are more effective than EFV and other regimens for viral suppression at 24, 48 and 96 weeks.

- All treatments tend to be comparable in terms of emergent serious adverse events, with exception of NVP (elevated risk)

- Limitation: Minimal data on DTG + TDF + XTC (SPRING-2)
What will be new in the 2015 ARV guidelines?

- 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
- Placement of INSTIs (DTG) and dose reduction options in 1\textsuperscript{st} and 2\textsuperscript{nd} line therapy
- PrEP recommended as an additional prevention choice for all people at substantial risk of HIV infection (> 3% incidence)
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%

---

Fig. 2. Median pre-treatment CD4 count and proportion of people living with HIV in Brazil who initiated ART according to the last CD4 count result before initiating ART, by year, 2009–2014

Fig. 7. Number of children newly initiating ART by age group in Uganda
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.

**Core Group Co-Chairs**
- Wafaa El-Sadr (ICAP and Columbia University; USA)
- Yogan Pillay (SA MoH)

**Guideline Development Group Co-Chairs**
- Elaine Abrams (ICAP, and Columbia University, USA)
- Serge Eholie (ANEPA/Treichville Hospital, Abidjan, Côte d’Ivoire)
- Anthony Harries (the Union; UK)
- Fabio Mesquita (Brazil MOH)

**WHO Department**
- Gottfried Hirnschall
- Andrew Ball
- Rachel Baggaley
- Rachel Beanland
- Marco Vitoria
- Martina Penazzato
- Shaffiq Essajee
- Nathan Ford
- Eyerusalem Kebede Negussie
- Alice Armstrong
- Francoise Renaud
- Bob Grant (consultant)
- Michelle Rodolph
- Annabel Baddeley, Alberto Mattelli,
- Haile Getahun

**Other Contributors**
- Temprano, START research teams
- The University of California, San Francisco, University of Basel
- Global Evaluation Service (GES)
- The HIV Modelling Consortium
- AFROCAB, APN+, AHF Ukraine, ICW, Vialibre, Pangaea
- The Global Network of People living with HIV/AIDS
- Avenir Health
- CDC
- PEPFAR
- Bill and Melinda Gates Foundation
## WHO ARV Guidelines Evolution 2002 to 2015

### When to start

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>CD4 ≤200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200 - Consider 350</td>
<td>CD4 ≤ 350 - Regardless CD4 for TB</td>
<td>CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC</td>
<td>CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC</td>
</tr>
</tbody>
</table>

### Earlier initiation

<table>
<thead>
<tr>
<th>1st Line ART</th>
<th>8 options - AZT preferred</th>
<th>4 options - AZT preferred</th>
<th>8 options - AZT or TDF preferred - d4T dose reduction</th>
<th>6 options &amp; FDCs - AZT or TDF preferred - d4T phase out</th>
<th>1 preferred option &amp; FDCs - TDF and EFV preferred across all pops</th>
<th>Towards Treat All Adolescents age band</th>
</tr>
</thead>
</table>

### Simpler treatment

|----------------|-----------------------------|---------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------------------------|

### Less toxic, more robust regimens

<table>
<thead>
<tr>
<th>3rd Line ART</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>DRV/r, RAL, ETV</th>
<th>DRV/r, RAL, ETV</th>
<th>_encourage HIV DR to guide</th>
</tr>
</thead>
</table>

### Viral Load Testing

|                | No                          | No (Desirable)                 | Yes (Tertiary centers)                      | Yes (Phase in approach)                     | Yes (preferred for monitoring, use of PoC, DBS) | Support for scale up of VL using all technologies |

Better and simpler monitoringz