New Directions in the 2015 Consolidated ARV Guidelines Update

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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

Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan 2014 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

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

Clinical

Operational & Service Delivery

Programmatic Prioritization
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

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

2005-2010

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

HPTN 052: reduction of HIV transmission among HIV serodiscordant couples and risk of TB in adults (impact on HIV incidence)

2010-2013

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

2015

1995-2005

2005-2010

2010-2013

2015

World Health Organization
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>WHAT IS EXPECTED IN 2015 ART GUIDELINES?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>ART initiation at any CD4</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+)</td>
</tr>
<tr>
<td>Adolescents (10-19 year old)</td>
<td>ART initiation at any CD4</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</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>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**
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>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: Tau² = 0.75; Chi² = 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)

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)

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**Grade 3 / 4 SAEs**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.96 [0.40, 2.01]</td>
</tr>
</tbody>
</table>

**Hepatic SAE**

- **Clinical trial**
  - Risk of hepatic & 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)

**Renal SAE**

- **Clinical trial**
  - Risk of hepatic & 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)

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CI confidence interval; IV, inverse variance; RCT, randomised controlled trial
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

*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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPERGAY – on demand Truvada (MSM – France &amp; Canada)</td>
<td>86% (39; 99)</td>
</tr>
<tr>
<td>PROUD – daily oral Truvada (MSM – United Kingdom)</td>
<td>86% (62; 96)</td>
</tr>
<tr>
<td>Partners PrEP – daily Truvada (Discordant couples – Kenya, Uganda)</td>
<td>75% (55; 87)</td>
</tr>
<tr>
<td>Partners PrEP – daily oral Tenofovir (Discordant couples – Kenya, Uganda)</td>
<td>67% (44; 81)</td>
</tr>
<tr>
<td>TDF2 – daily Truvada (Heterosexuals men and women - Botswana)</td>
<td>62% (22; 84)</td>
</tr>
<tr>
<td>iPrEx – daily Truvada (MSM - America’s, Thailand, South Africa)</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>FEMPrEP – daily Truvada (Women – Kenya, South Africa, Tanzania)</td>
<td>6% (-52; 41)</td>
</tr>
<tr>
<td>MTN003/VOICE – daily Truvada (Women – South Africa, Uganda, Zimbabwe)</td>
<td>-4% (-49; 27)</td>
</tr>
<tr>
<td>MTN003/VOICE – daily Viread (Women - South Africa, Uganda, Zimbabwe)</td>
<td>-49% (-129; 3)</td>
</tr>
<tr>
<td>CAPRISA 004 – coital Tenofovir gel (Women – South Africa)</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>MTN003/VOICE – daily Tenofovir gel (Women – South Africa, Uganda, Zimbabwe)</td>
<td>15% (-21; 40)</td>
</tr>
<tr>
<td>FACTS 001 – coital Tenofovir gel (Women – South Africa)</td>
<td>0% (-40; 30)</td>
</tr>
</tbody>
</table>
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 Socías, 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 1st and 2nd 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%
### Core Group Co-Chairs
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- Yogan Pillay (SA MoH)

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### Other Contributors
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- The University of California, San Francisco
- University of Basel
- Global Evaluation Service (GES)
- The HIV Modelling Consortium
- AFRO Cab, APN+, AHF Ukraine, ICW, Vialibre, Pangaea
- The Global Network of People living with HIV/AIDS
- Avenir Health
- CDC
- PEPFAR
- Bill and Melinda Gates Foundation

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.
## WHO ARV Guidelines Evolution 2002 to 2015

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</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 350</td>
<td>CD4 ≤ 500</td>
<td>Towards Treat All Adolescents age band</td>
</tr>
<tr>
<td><strong>1st Line ART</strong></td>
<td>8 options - AZT preferred</td>
<td>4 options - AZT preferred</td>
<td>8 options - AZT or TDF preferred</td>
<td>6 options &amp; FDCs - AZT or TDF preferred</td>
<td>1 preferred option &amp; FDCs - TDF and EFV preferred across all pops</td>
<td>Continue with FDC and harmonization across age bands</td>
</tr>
<tr>
<td><strong>2nd Line ART</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV</td>
<td>DRV/r, RAL, ETV</td>
<td>Encourage HIV DR to guide</td>
</tr>
<tr>
<td><strong>3rd Line ART</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV</td>
<td>DRV/r, RAL, ETV</td>
<td>Support for scale up of VL using all technologies</td>
</tr>
<tr>
<td><strong>Viral Load Testing</strong></td>
<td>No</td>
<td>No (Desirable)</td>
<td>Yes (Tertiary centers)</td>
<td>Yes (Phase in approach)</td>
<td>Yes (preferred for monitoring, use of PoC, DBS)</td>
<td>Better and simpler monitoring</td>
</tr>
</tbody>
</table>

- **Earlier initiation**
  - Earlier initiation aims to treat all adolescents in the same age band, considering CD4 counts.
  - **1st Line ART**
    - D4T dose reduction and phase out in 2010.
  - **2nd Line ART**
    - Greater number of options in 2014.
  - **3rd Line ART**
    - HAART prescribing continues.

- **Less toxic, more robust regimens**
  - **1st Line ART**
    - D4T dose reduction and phase out.
  - **2nd Line ART**
    - More stable FDCs.
  - **3rd Line ART**
    - Phase in approach.

- **Viral Load Testing**
  - **1st Line ART**
    - Viral load testing becomes desirable.
  - **2nd Line ART**
    - Use of PoC, DBS.
  - **3rd Line ART**
    - Preferred for monitoring.

- **Towards Treat All Adolescents age band**
  - Treatment is tailored towards adolescents in the specified age bands.