WHO guidelines on the use of CD4, Viral Load and EID tests for initiation and monitoring of ART

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Treatment and Care Unit
WHO, Geneva
The 2013 Consolidated ARV Guidelines: Key recommendations

**Clinically relevant**

- Earlier initiation of ART (CD4 count \(\leq 500\) cells/mm\(^3\)) for adult s & adolescents
- Immediate ART for children below 5 years
- More potent regimens for children < 3 years (LPV/r)
- Immediate & lifelong ART for all pregnant and breastfeeding women (Option B/B+)
- Simplified, less toxic 1\(^{st}\)-line regimens (TDF/XTC/EFV)

**Operationally relevant**

- Use of Fixed Dose Combinations (FDCs)
- Improved patient monitoring with increased use of viral load
- Recommend task shifting, decentralization, and integration
- Community based testing and ARV delivery
Making Impact in Countries – 2013-14 ARV Policies (% responding yes, by region)

Policy uptake in 58 WHO focus countries end 2014, by region

Uptake of 2013 recommendations as of Oct 2014
Access to ART worldwide has significantly increased but coverage still very heterogeneous...

Hill et al. CROI 2015 [abstr 1118]
Even in settings with good testing & ART coverage, treatment cascades still show important leakages...

**Cascade of HIV care – Sub-Saharan Africa**

**Cascade of HIV Care – Brazil, 2013**

**Cascade of HIV care – Russia**

**Cascade of HIV care – British Columbia (CA)**

**Hill et al. CROI 2015 [abstr 1118]**
Innovations in Diagnostics

- CD4
- VL
- EID
Treatment initiation still late in the large majority of countries

Median CD4 count at start in 2011
Median CD4 count at start in 2012 (data for some countries extrapolated)

Courtesy: D Cooper, IAC 2014
POC CD4 implementation across sub-Saharan Africa

- **Ethiopia**: 104 sites
- **Kenya**: 77 sites
- **Uganda**: 303 sites
- **Tanzania**: 445 sites
- **Zambia**: 68 sites
- **Zimbabwe**: 276 sites
- **Malawi**: 126 sites
- **Mozambique**: 132 sites
- **Swaziland**: 77 sites
- **Lesotho**: 42 sites
### Impact of Point of care CD4 on linkage/retention in HIV care

<table>
<thead>
<tr>
<th>Name</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faal</td>
<td>2.81 (1.39, 5.69)</td>
</tr>
<tr>
<td>Jani</td>
<td>1.86 (1.37, 2.51)</td>
</tr>
<tr>
<td>Patten</td>
<td>1.48 (0.93, 2.36)</td>
</tr>
<tr>
<td>Muchedzi</td>
<td>1.84 (1.51, 2.25)</td>
</tr>
<tr>
<td>Matambo</td>
<td>2.88 (2.40, 3.45)</td>
</tr>
<tr>
<td>Larson</td>
<td>1.48 (1.17, 1.87)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.95 (1.51, 2.53)</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.

- Odds of linking to care increased.
- Time to testing reduced by 9 days.
- Time from testing to receiving the result was reduced by 17 days.
CD4 changes when virally suppressed in S. Africa

>90% of suppressed patients maintained CD4+ cell counts >200 cells/µl up to 10 years

97% (133/137) of CD4 declines <200 cells/µl were transient
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>CD4 declines (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philipps</td>
<td>UK</td>
<td>0.15 (0.14, 1.31)</td>
</tr>
<tr>
<td>Stephan</td>
<td></td>
<td>2.11 (0.10, 0.95)</td>
</tr>
<tr>
<td>Gale</td>
<td></td>
<td>3.24 (3.30, 6.19)</td>
</tr>
<tr>
<td>Girard</td>
<td></td>
<td>0.06 (0.05, 0.49)</td>
</tr>
<tr>
<td>Whitlock</td>
<td></td>
<td>0.26 (0.05, 0.49)</td>
</tr>
<tr>
<td>Reynolds</td>
<td></td>
<td>0.58 (0.26, 4.63)</td>
</tr>
<tr>
<td>Ford</td>
<td></td>
<td>1.31 (0.21, 0.93)</td>
</tr>
<tr>
<td>Davies</td>
<td></td>
<td>0.04 (0.04, 0.21)</td>
</tr>
<tr>
<td>Chow</td>
<td>Australia</td>
<td>0.02 (0.02, 0.22)</td>
</tr>
<tr>
<td>Duncan</td>
<td>UK</td>
<td>0.90 (0.20, 2.08)</td>
</tr>
<tr>
<td>Kitizo</td>
<td>Kenya</td>
<td>2.61 (0.90, 5.20)</td>
</tr>
<tr>
<td>Ahn</td>
<td>Asia</td>
<td>1.27 (0.77, 1.89)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.49 (0.25, 0.73)</td>
</tr>
</tbody>
</table>

Meta-analysis of 11 studies

<1% of patients who were virologically suppressed experienced a CD4 decline
Safe to scale down CD4 for monitoring when VL

• These data are consistent with findings from trial and observational studies in Western settings that CD4 measures rarely change in virologically suppressed patients.

• CD4 remains a critical diagnostic tool for risk stratification and ART and prophylaxis decisions.

• In settings where both CD4 and viral load are available, countries could consider reducing or eliminating CD4 for monitoring.
When should CD4 be used for initiation & monitoring?

- **CD4 for initiation: Point of care CD4:**
  - Increased access to testing in rural and remote areas
  - Reduced turn around time for results
  - Potential decrease in LTFU

- **2013 ARV Guidelines:**
  - CD4 monitoring every 6 months on ART

- **2014 Supplement: Changing role of CD4**
  - “HIV viral load when available is a more reliable tool for monitoring adherence...than CD4..”
  - CD4 for screening for opportunistic infections
2015 - CD4 guidelines new questions

• 1.1 Does point of care CD4 count improve linkage to HIV care and timeliness of ART initiation?

• 1.2 In individuals with HIV who have achieved viral suppression on ART is CD4 count and VL annually more effective than VL annually?
**WHO 2013 Recommendations: Monitoring for ART Response**

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure</td>
<td><em>Strong recommendation, low-quality evidence</em></td>
</tr>
<tr>
<td>If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure</td>
<td><em>Strong recommendation, moderate-quality evidence</em></td>
</tr>
</tbody>
</table>

**Threshold for defining virological failure:**

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1000 cpm</td>
<td>1000 cpm</td>
</tr>
</tbody>
</table>
### Immunological and clinical criteria

<table>
<thead>
<tr>
<th>Pop</th>
<th>Viral load</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>&gt;5000</td>
<td>68.9%</td>
<td>92.1%</td>
<td>27.0%</td>
<td>98.6%</td>
</tr>
<tr>
<td>Adults</td>
<td>50-4,999</td>
<td>55.6%</td>
<td>74.5%</td>
<td>29.8%</td>
<td>89.6%</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt;10,000</td>
<td>16.8%</td>
<td>95.5%</td>
<td>15.0%</td>
<td>96.0%</td>
</tr>
<tr>
<td>Children</td>
<td>&gt;5,000</td>
<td>4.5%</td>
<td>99.3%</td>
<td>54.9%</td>
<td>85.5%</td>
</tr>
<tr>
<td>Children</td>
<td>&gt;400</td>
<td>6.3%</td>
<td>97.7%</td>
<td>20.0%</td>
<td>91.8%</td>
</tr>
</tbody>
</table>

Rutherford *et al*, IAS 2014

Immunological and clinical monitoring have poor sensitivity and lower positive predictive value for identifying virologic failure.
Targeted viral load monitoring (suspected clinical or immunological failure)

Routine viral load monitoring (early detection of virological failure)

Test viral load

Viral load >1000 copies/ml

Evaluate for adherence concerns

Repeat viral load testing after 3–6 months

Viral load ≤1000 copies/ml

Maintain first-line therapy

Viral load >1000 copies/ml

Switch to second-line therapy

Rationale: Viral Load Monitoring
Viral load to reinforce adherence and confirm treatment failure

Bonner et al, JAIDS 2013
Implementation considerations

• **ART access should be the first priority**: Lack of laboratory tests for monitoring treatment response should not be a barrier to initiating ART.

• Prioritization: If viral load availability is limited, it should be phased in using a targeted approach to confirm treatment failure.

• This may be particularly relevant in populations receiving ARVs to reduce HIV transmission, such as pregnant and breastfeeding women and in sero-discordant couples.
Viral Load Implementation

- Guidance for MoH
  - Phase in, planning, lab network
  - Overview of technologies
  - DBS use, cutoff at 1000cpm
  - Quality

Phase I: Planning
- Policies and Leadership
- Harmonization
- Algorithm
- Mapping and Forecasting
- Assess Capacity
- Costing
- Specimen and Product Selection
- Equipment Procurement

Phase II: Scale Up
- Phase In
- Human Resources
- Training and Supervision
- Quality Management System

Phase III: Sustainability
- Partner Harmonization
- M&E
- Data Collection
- Operational Research
Suggested Revisions Routine

ART Initiation

Test viral load 6 months

Viral load >1000 copies/ml

Adherence counselling

Repeat viral load testing after 3–6 months

Viral load ≤1000 copies/ml

Maintain first-line therapy

Viral load >1000 copies/ml

Switch to second-line therapy

Annual testing
Why do we want to detect early poor adherence?

- Patients who had a VL taken at month 3 versus at month 6 were 22% less likely to experience virological failure and 27% less likely to be switched to a second line regimen.

- For each additional month of delay in taking the first viral load (between 2.5 and 9 months) the risk of virological failure increased by 9% and the risk of treatment switching increased by 14%.
Specimen Type and Operational Considerations

**Plasma specimens**
- The gold standard to determine viral failure
- Must be prepared from anticoagulated EDTA-whole blood (venous) within six hours of blood collection (if left at room temperature, 24 hours at 2–8°C) or according to the manufacturer’s instructions
- Prepared plasma can be stored at room temperature for up to 24 hours, at 2–8°C for up to 5 days and −20°C to −80°C for longer periods
- Can be used accurately on all the existing laboratory-based platforms

**Dried blood spot specimens**
- Not considered biohazardous once dried
- Easier to transport and are not as time and temperature sensitive as EDTA-whole blood or plasma specimens
- Can be prepared using a precision pipette/microcapillary EDTA-venous blood or finger-prick blood specimen prepared using a measured microcapillary tube
- Can be prepared using Whatman 903, Munktell TNF, Ahlstrom Grade 226 DBS collection cards depending on the manufacturer’s instructions
Table 1. Provisional data on performance characteristics for commercially available molecular HIV viral load assays using dried blood spot specimens compared with plasma at 1,000 copies/ml cut-off

<table>
<thead>
<tr>
<th>Assay assessed</th>
<th>Sensitivity (mean %)</th>
<th>Specificity (mean %)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Molecular: Abbott RealTime HIV-1 (manual, m24sp and m2000sp) assays with m2000rt platform</td>
<td>95.24a</td>
<td>91.67a</td>
<td>1529</td>
</tr>
<tr>
<td>Biocentric: Generic HIV Charge Virale</td>
<td>94.86a</td>
<td>55.16a</td>
<td>531</td>
</tr>
<tr>
<td>bioMérieux: NucliSENS EasyQ® HIV-1 v2.0</td>
<td>84.37a</td>
<td>94.52a</td>
<td>1062</td>
</tr>
<tr>
<td>Roche Molecular Systems: COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 [free virus elution protocol]</td>
<td>81.02b</td>
<td>96.74b</td>
<td>229</td>
</tr>
<tr>
<td>HIV-1 RNA 1.0 Assay (kPCR)</td>
<td>90.97a</td>
<td>87.76a</td>
<td>144</td>
</tr>
</tbody>
</table>

Sources: aLara Vojnov et al., Clinton Health Access Initiative, unpublished manuscript on dried blood spot specimens with highly variable performance compared with plasma across the five available viral load technologies, 15 June 2014. bSergio Carmona and Zukiswa Mahlumba, South African National Health Laboratory Service, unpublished raw data using the new Roche COBAS® Ampliprep/TaqMan® system version 2.0 with the revised free virus elution (FVE) protocol and specimens processed within one week of collection, 18 June 2014; further research is required. Using the existing Roche COBAS® Ampliprep/TaqMan® system version 2.0 (SPEX) protocol, the results were different: sensitivity: 99.33%, specificity 43.86%, n = 2314 (Lara Vojnov et al., Clinton Health Access Initiative).
Guidance on use DBS for Viral Load

• The use of dried blood spots for viral load testing is recommended if logistical constraints challenge the use of plasma.

• **Dried blood spots should be used with the same threshold of plasma for ART failure: 1,000 copies/ml.**

• Not all technologies should be used for viral load testing with dried blood spot samples.

• While the performance of dried blood spot samples is currently acceptable for most technologies, the lower acceptable limits for sensitivity and specificity are unclear.
QA Cycle for Implementing POCT

PHASE III: Evaluate, Improve, and Sustain
1. Post market surveillance
2. Use monitoring data for decision making
3. Advocacy and communication of best practices
4. Encourage social entrepreneurship and public private partnerships
5. Increase country ownership
6. Operational research

PHASE I: Planning Quality Improvement for HIV-related POCT
1. Engage Leadership
2. Establish the national QA/POCT coordination team
3. Define roles and responsibilities
4. Develop or review policies & incorporate QA into national plan
5. Define standards for quality for POCT
6. Conduct situational analysis
7. Develop and implement plan
8. Plan financial and human resources
9. Selection and assessment of sites
10. Selection of product

PHASE II: Implementation of Quality Assurance for POCT
1. Improve training and ensure certification of all POC Testers
2. Site supervision and certification
3. Implement QA Process Control
4. Strengthen and innovate QA-related documentation
5. Strengthen supply chain for QA
2015 VL Update Questions

• 2.1 In individuals receiving ART, is initial viral load testing at 3 months more effective than at 6 months?

• 2.2 In individuals ART is dried blood spot testing at VL threshold > 1000 cpm as effective as VL > 1000 cpm using plasma?

• 2.3 In individuals on ART, 20% misclassification of viral load result using dried blood spot (DBS) testing acceptable? (Modelling question)
Infant Testing Algorithm

HIV-exposed infant or child <18 months
- Conduct diagnostic viral test*
  - Viral test available
    - Positive
      - Infant or child is likely infected
        - <24 months: immediately start ART and repeat viral test to confirm infection
    - Negative
      - Infant or child is uninfected
        - Never breastfed
        - Ever breastfed or currently breastfeeding
          - Infant or child remains at risk of acquiring HIV infection until complete cessation of breastfeeding
          - Regular and periodic clinical monitoring
  - Viral test not available
  - Infant develops signs or symptoms suggesting HIV
  - Infant remains well and reaches 9 months of age
    - Conduct HIV antibody test at approximately 9 months of age
      - Viral test not available
      - Positive
        - Infant or child is HIV infected
          - Start ART and repeat viral test to confirm infection
      - Negative
        - Viral test not available: assume infected if sick; assume uninfected if well
          - HIV unlikely unless still breastfeeding
          - Repeat antibody test at 18 months of age and/or 6 weeks after cessation of breastfeeding

*For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks). See also Table 5.1 on infant diagnosis.
*Start ART, if indicated, without delay. At the same time, retest to confirm infection.
*The risk of HIV transmission remains as long as breastfeeding continues.
Testing at birth

- Better retention in the cascade
- Earlier ART initiation
- Low sensitivity of virological testing at birth
- Increased cost

Diagram showing ART initiation under current recommendation of 6-week PCR test.
Negative Serology with early ART

We need to get the diagnosis right before ART is started

Payne H et al. CROI 2014

Negative Ab test while on ART does NOT mean NO HIV infection!!!
2015 EID Update Questions

- Does birth testing improve retention and ARV initiation?
- Can HIV exposure be confirmed using HIV rapid antibody tests (in HIV-exposed and -unexposed infants)?
- Can rapid HIV antibody tests be used to exclude HIV infection (in HIV-exposed and -unexposed infants)?
- Can HIV infection in HIV-exposed and -unexposed children aged 18 months and older be diagnosed using HIV rapid antibody tests?
2015 ARV Guidelines Timeline

- **Core Group meeting**: Oct 20-21 2014
- **PADO 2**: Dec 8-9
- **B+**: Jan 14-16
- **Systematic reviews**
  - Values and preferences
  - Community consultations
  - Modelling
  - (Dec – May, 2015)
- **Programmatic Update IAS July 2014**
- **Guideline Development Group Meetings**: Clinical/operational
  - June 1-5 2015
  - June 16-19 2015
- **Submission to GRC Sept 2014**
- **Updated Consolidated ARV Guidelines Launch**: Dec 2015
- **Supplement launch WAD**: Dec 1 2014
- **Publication Process**
- **Core Group July 23-24**
- **Programmatic Chapter**
- **Values and preferences**
- **Civil society representation**
- **CSR格**
- **Community consultation**
- **Vancouver IAS July 19-22**
- **PEER REVIEW**