WHO 2015 update of consolidated ARV guidelines
What is new?

Meg Doherty
WHO HQ
Outline

• What’s new in ARV Guidelines

• Diagnostics and monitoring
  • CD4
  • Viral load
  • Infant testing (EID, NAT, RDTs)
  • HIVDR

• Moving forward
Progress in access to antiretroviral therapy: 2000–2015

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

ART coverage

- Africa
- Americas
- South-East Asia
- Europe
- Western Pacific
- Eastern Mediterranean

“15 BY 15”
A GLOBAL TARGET ACHIEVED

- 2000: 2%
- 2004: 7%
- 2008: 15%
- 2012: 32%
- 2014: 40%
Some key messages from the 2015 WHO ARV guidelines

• Treat all (at any CD4) - PLHIV across all ages, but the sickest remain a priority (symptomatic disease and CD4 < 350).

• DBS for VL, conditional recommendation for birth testing, POC EID, guidance for infant testing using RDTs,

• Phased introduction of optimized drug regimens and formulations (DTG, low dose EFV, DRV/r).

• Care packages to optimize the care cascade (reduce late presentation, improve retention).
WHO Consolidated guidelines on the use of ARV drugs for treating and preventing HIV
Global number of PLHIV

16 million

+13 million

+9 million

Treatment gap with expanded eligibility criteria (Treat all)

~ 37 million

PLHIV currently on ART

Cost 31 billion USD per year by 2020; 50% treatment cost

Treatment gap based on 2013 WHO ART guidelines (CD4 < 500)
ART monitoring: CD4

- ART should be initiated independently of CD4 cell count
- CD4 cell count is important at baseline and in case of failure
- CD4 cell count at the point of care can be used to prioritize patients in urgent need of linkage and ART (*conditional, low*)
- CD4 cell count monitoring can be stopped if viral load is available (*conditional, low*)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>patients</th>
<th>CD4 declines (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips</td>
<td>UK</td>
<td>166</td>
<td>0.15 (0.14, 1.31)</td>
</tr>
<tr>
<td>Stephan</td>
<td>Multiple</td>
<td>230</td>
<td>0.11 (0.10, 0.96)</td>
</tr>
<tr>
<td>Gale</td>
<td>USA</td>
<td>832</td>
<td>4.64 (3.30, 6.19)</td>
</tr>
<tr>
<td>Girard</td>
<td>Multiple</td>
<td>449</td>
<td>0.06 (0.05, 0.49)</td>
</tr>
<tr>
<td>Whitlock</td>
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<tr>
<td>Reynold</td>
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<tr>
<td>Ford</td>
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<tr>
<td>Davies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chow</td>
<td>Australia</td>
<td>744</td>
<td>0.02 (0.02, 0.22)</td>
</tr>
<tr>
<td>Duncan</td>
<td>UK</td>
<td>392</td>
<td>0.90 (0.20, 2.08)</td>
</tr>
<tr>
<td>Kitis</td>
<td>Kenya</td>
<td>209</td>
<td>2.61 (0.90, 5.20)</td>
</tr>
<tr>
<td>Ann</td>
<td>Asia</td>
<td>1538</td>
<td>1.27 (0.77, 1.89)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.49 (0.25, 0.73)</td>
</tr>
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</table>

<0.5% CD4 changes if virally suppressed
ART monitoring: Viral Load

- Viral load is recommended as the preferred approach to diagnose and confirm treatment failure
  - Viral load failure is defined as persistent viral load > 1000 copies/ml
  - Viral load should be measured at 6M, 12M then every 12M (*conditional, very low*)
  - Dried blood spots can be used to determine viral load (*conditional, low*)
Recommendations for diagnosis of treatment failure

• Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure\(^a\) (strong recommendation, low quality evidence).

• If viral load is not routinely available, CD4 cell count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate quality evidence).

• Virological failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three month interval, with adherence support between measurements) after at least six months of starting a new ART regimen.

• Dried blood spot specimens using venous or capillary whole blood can be used to determine HIV viral load. A threshold of 1000 copies/ml can be used to determine virological failure when using dried blood spot samples, as defined for testing in plasma\(^a\) (conditional recommendation, low quality evidence). **NEW**

\(^a\) Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.
Recommendations for routine monitoring

• Routine viral load monitoring can be carried out at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting (conditional recommendation, very low quality evidence).

• In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virologically suppressed (conditional recommendation, low quality evidence).

\[ a \] Viral load testing should be performed early after initiating ART (within 6 months), at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible.

\[ b \] WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measures below 1000 copies/ml). For service delivery recommendations in these guidelines (Section 6), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.
Performance of assay type using DBS compared to plasma using VL threshold of 1000 copies/ml

<table>
<thead>
<tr>
<th></th>
<th>Abbott RealTime</th>
<th>Biocentric Charge Virale</th>
<th>bioMerieux Nucleisens</th>
<th>Roche TaqMan FVE</th>
<th>Roche TaqMan SPEX</th>
<th>Siemens kPCR</th>
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<tbody>
<tr>
<td><strong>Sensitivity^a</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% (82-99%)</td>
<td>95% (71-99%)</td>
<td>84% (79-89%)</td>
<td>88% (83-91%)</td>
<td>99% (97-100%)</td>
<td>91% (69-98%)</td>
</tr>
<tr>
<td><strong>Specificity^</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92% (79-, 97%)</td>
<td>55% (35-74%)</td>
<td>95% (86-98%)</td>
<td>97% (81-100%)</td>
<td>44% (18-74%)</td>
<td>88% (75-94%)</td>
</tr>
</tbody>
</table>

* a Pooled estimates of sensitivity and specificity based on published data up to June 2015
## Comparative Analysis: CD4 cell count vs HIV viral load

<table>
<thead>
<tr>
<th>Major Parameters</th>
<th>CD4</th>
<th>Viral Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART impact on HIV morbidity &amp; mortality</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ART impact on HIV transmission (individual level)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Management of OI prophylaxis &amp; late presenters</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Support to ART adherence</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Support for monitoring/prevention of ARV drug resistance</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Accuracy in establishment of ART failure</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Early detection of ART failure</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lower complexity and cost</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Current availability as PoC</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

HIV/AIDS Department
The third 90: Monitoring Treatment & implementing VL testing

Routine VL in 144 LMIC = 78%; Targeted VL = 22%

Guidance to support scale-up

- Forecasting diagnostic needs
- VL scale-up guidance
- Recommendations on DBS, EID, POC
- Handbook on QA for POCT (2 meetings to disseminate)
- Support to accreditation (SLIPTA/SLMPTA in AFRO & EURO)
- Toxicity monitoring
Implementation considerations: scaling up viral load testing

- Consider the various diagnostic options
- Review the use of viral load monitoring in the context of alternative patient monitoring strategies (CD4, VL for confirmation of failure)
- Provide additional adherence support in the context of earlier ART initiation
- Develop treatment literacy on the use and meaning of viral load
- Ensure an adequate supply of second-line ARV drugs
- Implement quality assurance strategies
Paediatric Diagnostic Recommendations

Test earlier
Test closer
Treat earlier
WHO 2010-13 infant testing algorithm

Is this algorithm still appropriate?
Continue to have theoretical concerns attached to the impact that ARVs may have on the test performance at 6 weeks.

Lack of robust evidence to reassure us.

Potential shift to enhanced prophylaxis may further complicate this scenario.

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**B. Virological testing at 6 weeks with DBS (compared to whole blood)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Characteristics</th>
<th>ARV Exposure</th>
<th>Index Test</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loelawat et al 2000 (Thailand)</td>
<td>Cohort of 162 paired samples at 2 months. Non-breastfeeding</td>
<td>Monotherapy of short-course ZDV OR combo short course ZDV and d4NVP</td>
<td>Amplicor HIV-1 DNA v1.5</td>
<td>Whole blood</td>
</tr>
<tr>
<td>Lilian et al 2010 (South Africa)</td>
<td>Cross-sectional study of 125 infants (4-8 weeks). Unknown breastfeeding</td>
<td>d4NVP to mother and infant</td>
<td>Nuclisens RNA</td>
<td>DNA PCR on whole blood</td>
</tr>
<tr>
<td>Yapo et al 2013 (Cote d'Ivoire)</td>
<td>Cross-sectional within cohort of 71 infants (4-8 weeks). 49/71 were breast/feeding</td>
<td>Maternal Regimen: NVP pre partum followed by ZDV/3TC post partum (3), ZDV/3TC/NVP (32), TDF/FTC/NVP; 4T/3TC/NVP (9), ZDV/3TC/ABC (1)</td>
<td>Biocentric (DNA)</td>
<td>Biocentric DNA Kit on cell pellets</td>
</tr>
</tbody>
</table>

**Risk of bias**

Proportion of studies with low, high, or unclear risk of bias (n=3)

**Applicability**

Proportion of studies with low, high, or unclear concerns about applicability (n=3)

**Sensitivity**

99.43 (98.27, 100)

**Specificity**

99.63 (99.11, 100)
Minimising mortality and maximizing programme outcomes with NAT at birth

Addition of nucleic acid testing (NAT) at birth to the existing EID testing approaches can be considered to identify HIV infection in HIV-exposed infants (conditional recommendation, low-quality evidence)

Adoption should ensure:

- **collection of data** on performance and feasibility of birth testing alongside implementation
- improvement of **uptake and retention** in the testing to treatment cascade
- **active tracking of infants with negative NAT at birth** to ensure they return at 6 weeks for retesting and cotrimoxazole initiation.
- **re-testing of infants who test positive** at birth with a second specimen as soon as possible (ART should be started immediately after the first positive test and can be stopped if second specimen is negative).
POC NAT

Nucleic acid testing (NAT) technologies that are developed and validated for use at or near to point of care can be used for early infant HIV testing. (Conditional recommendation, low-quality evidence)

• To complement and enhance conventional testing approaches by offering a flexible and faster testing approach that could be implemented by non-laboratory staff.

• Decentralization of ART or strengthening of referral systems for ART initiation remain of critical importance to ensure impact on infant outcomes.

• Targeted operational research is needed to address existing knowledge gaps resulting from the limited experience to date.
RDTs

- **Performance** of the RDTs to assess HIV-exposure or HIV-infection differs based on age.
- In children **4-18 months** the sensitivity of RDTs is low.
- Use of RDT to **test the mother** should be prioritised.

- Rapid diagnostic tests (RDTs) for HIV serology **can be used to assess HIV exposure in infants less than 4 months of age**. HIV-exposure status in infants and children 4-18 months of age should therefore be ascertained by undertaking HIV serological testing in the mother (Conditional, low-quality evidence).
- Rapid diagnostic tests (RDTs) for HIV serology **can be used at 9 months to rule out HIV infection** in asymptomatic HIV-exposed infants. (Conditional recommendation, low-quality evidence).
- Rapid diagnostic tests (RDTs) for HIV serology **can be used to diagnose HIV infection in children older than 18 months following** the national testing strategy. (Strong recommendation, moderate-quality evidence).
<table>
<thead>
<tr>
<th>Age group</th>
<th>Known HIV-exposed</th>
<th>Unknown HIV exposure status and breastfeeding</th>
<th>Unknown HIV exposure status and not breastfeeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 months</td>
<td>Not useful as exposure is known and RDT cannot determine infection status</td>
<td>Test mother If mother not available, RDT in the child can reliably assess exposure status</td>
<td>Test mother If mother is not available, RDT in the child reliably determines exposure status</td>
</tr>
<tr>
<td>5-8 months</td>
<td>Not useful as exposure is known and RDT cannot determine infection status</td>
<td>Test mother If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. Infants with positive RDT will still need NAT to confirm infection status. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
<td>Test mother If mother is not available, RDT for the child does not fully rule out exposure status. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
</tr>
<tr>
<td>9-18 months</td>
<td>RDT useful to rule out established HIV infection Infants with positive RDT will still need NAT to confirm infection status Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
<td>Test mother If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. RDT useful to rule out established HIV infection Infants with positive RDT will still need NAT to confirm infection status. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
<td>Test mother If mother not available RDT in the child does not fully rule out exposure status. RDT useful to rule out established HIV infection Infants with positive RDT will still need NAT to confirm infection status. Infants with negative RDT who are not breastfeeding can be considered uninfected. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
</tr>
<tr>
<td>&gt;18 months</td>
<td>Serological testing (including RDT) is recommended to assess HIV infection status unless still breastfed If still breastfed NAT should be provided 4-6 weeks after cessation of breastfeeding.</td>
<td>Test mother If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. RDT useful to rule out established HIV infection Infants with positive RDT will still need NAT to confirm infection status. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
<td>Test mother If mother not available RDT in the child does not fully rule out exposure status. RDT useful to rule out established HIV infection Infants with positive RDT will still need NAT to confirm infection status. Infants with negative RDT who are not breastfeeding can be considered uninfected. If sick and mother is not available, perform NAT directly to assess HIV infection status.</td>
</tr>
</tbody>
</table>
The third 90: Tracking, preventing and reacting to HIVDR

From 2005-2015:

- 200 rounds of EWI
- Surveys: PDR, ADR
- Lab network ➔ 31 HIVDR labs
- Guidance and tools
- Global platform for exchange and coordination (HIVResnet)
- Global Action Plan in development

WHO HIVDR Laboratory Network December 2015

Labs: Laboratories accredited by WHO (plasma)
- Laboratories accredited by WHO (plasma and DBS)
- Laboratories undergoing assessment for accreditation

WHO Strategy Meeting, 10-11 February 2016
HIV Drug Resistance (HIVDR)

- Surveillance data from 2004-2010 revealed pre-treatment (PDR) HIVDR increased over time in LMIC and estimated that to be 6.8% in 2010.

- Increase levels of **NNRTI PDR** have emerged in several LMIC including: Angola (16%), Cuba (22%), Papua New Guinea (16%), Argentina (11%), Mexico (11%), Botswana (10%). A recent survey from another African country show NNRTI PDR >15%.

- Wide implementation of newly released WHO HIV Consolidated Guidelines on Treat All and PrEP, while reducing HIV incidence, are likely to further increase HIVDR prevalence.

- While the concern of HIVDR should not stop from providing ARVs to all in need, the long-term implications of earlier initiation on adherence and HIVDR need to be closely monitored.

- WHO recommends that ART scale up should be accompanied by **routine HIVDR Surveillance; no indication for individual HIVDR**
WHO HIVDR Surveillance and Monitoring

- Early Warning Indicators
- Pre-treatment HIVDR
- HIVDR surveillance and Monitoring
- Acquired HIVDR
- Infants <18 months ART-naive

Generic Protocol for surveillance of initial drug-resistant HIV-1 among children < 18 months of age newly diagnosed with HIV
Major WHO Normative Documents on HIV Treatment, Care and Prevention in 2015

2015

- Technical Update on PrEP
- Consolidated Guidelines on HIV Testing Services
- 2014-2018 Forecasts for ARVs and HIV diagnostics in LMICs
- Guidelines on When to Start ART and PrEP
- Early Country Experiences with Treat All Policy
- 2015 Consolidated ARV Guidelines
- Viral load Update
- VMMC for HIV Prevention in East and Southern Africa
- Consolidated Strategic Information Guidelines
- Transgender People and HIV
- IATT Option B/B+ Framework
- Monitoring Tool Targets for Key Populations
- Implementing HIV and STI Programmes with MSM
- Handbook on QA for POCT
- HIV and Young Key Populations (MSM, PWID, PWSS, TG)

2016
Moving forward

• Continue to scale-up VL; as integral to the success of differentiated models of care
• DBS to be rolled out to support scale-up
• Evaluations of EID in context of ARVs and at birth
• POC EID platforms to improve access to EID
• Support to countries to implement new guidance around use of RDTs in infants/young children
• HIVDR surveillance – support for PDR & ADR with report in 2016
• QA support
**Acknowledgements**

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<table>
<thead>
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</thead>
<tbody>
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<tr>
<td></td>
<td>Annabel Baddaley</td>
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<td>Haileyesus Getahun</td>
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</table>
Framework for differentiated approach to care

- Different Care package elements for different PLHIV categories.
  - Patients presenting well
  - Patients presenting with advanced HIV infection
  - Stable patients
  - Patients on ART with complex problems
Frequency of clinic and ARV pickup visits

• Less frequent clinic visits (3-6 months) *(strong, moderate)* and

• Less frequent medication pick up visits (3-6 months) *(strong, low)* for patients stable on ART can contribute in reducing long queues in facilities and reduce cost of care for patients.

• Trained and supervised lay providers can distribute ARV in community settings *(strong, low)*