The HIV Treatment Cascade in Children and Adolescents: an update

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About 5,600 new HIV infections a day in 2014

- About 66% are in Sub Saharan Africa

- About 600 are in children under 15 years of age

- About 5,000 are in adults aged 15 years and older, of whom:
  - almost 48% are among women
  - about 30% (1500) are among young people (15-24)
Estimated number of AIDS-related deaths among children (aged 0–9), adolescents (aged 10–19) and young people (aged 20–29) over the period 2001–2013

Source: UNAIDS estimates, 2013
On World AIDS Day, December 2014, UNAIDS made a Declaration

By 2020:

- 90% of HIV-positive children’s statuses are known
- 90% of children diagnosed HIV-positive are on ART
- 90% of children on treatment are virally supressed by 2020

Celletti F et al. The Lancet. 2015. Vol 2;e80-81

The HIV Treatment Cascade

Was proposed by Gardner et al in 2011:

cumulative effect of the various steps from being diagnosed to achieving viral load suppression

Steps:
1. Making the diagnosis
2. Linking to care
3. Retaining in care and starting ART
4. Maintaining adherence and achieving Viral Load suppression
Cascade of HIV care – Sub-Saharan Africa 2013
(15 – 45 years old)

- HIV Positive People (All ages): 23.5 million
- Diagnosed (Age 15 - 49): 51%
  - 12.0 million
  - Breakpoint 1
- Linked to care: 43%
  - 10.0 million
  - Breakpoint 2
- Retained in care: 32%
  - 7.5 million
  - Breakpoint 3
- On ART: Viral Suppression (<500, <350, <200)

Viral suppression Data from: Botswana, Burkina Faso, Mali, Cameroon, Cote d’Ivoire, Kenya, Senegal, Uganda, Malawi, Mozambique, Nigeria, Senegal,

Cumulative retention of children at each stage of care after HIV diagnosis

![Bar chart showing cumulative retention at each stage after HIV diagnosis](image)
Early Infant Diagnosis

Early antiretroviral therapy reduced HIV-related mortality in children living with HIV by 75%.

Yet, in 2013, only 42% of infants born to mothers living with HIV in low- and middle-income countries received this test within two months as recommended by WHO.
Barriers and Challenges

- Limited laboratories and clinics available that meet paediatric care needs.

- Many children do not receive their conclusive HIV test at the end of breastfeeding when the risk of vertical transmission ends—a lost opportunity to link those who may have seroconverted into care.

- Transportation costs—many families cannot afford the multiple visits to health centres needed to determine the HIV-status of babies exposed to HIV.

- Stigma and discrimination—some parents do not want their child tested due to fears about stigma against their child or themselves.

- Supply shortages—countries with high HIV prevalence often face shortages of supplies needed to diagnose and treat children living with HIV.

- Ultra sensitive tests needed for infants whose mothers on HAART
Progress / Achievements

- **New tests which are highly sensitive:**
  - study conducted in Mozambique
  - 25% of infants who tested negative at birth, found to be +ve with ultra sensitive tests

- **Point of care testing**
  - studies conducted in Malawi and Mozambique
  - decreased turnaround time for PCR results
  - Best result in those > 6 months

- **Oral fluid antibody test**
  - negative predictive value of 98%
  - Useful to rule out HIV
  - Found to be 100% acceptable to mothers

- **Lay personnel training**
New Recommendation (IAS 2015)

Should trained lay providers perform HIV testing services using HIV rapid diagnostic tests?

Studies identified: 1 RCT, 4 observational studies & 6 studies on values & preferences

Increased Uptake

- Uptake among ED patients was 57% (1,382/2,446) in the lay provider arm compared with 27% in the healthcare provider arm (643/2,409; RR: 2.12, 95% CI: 1.96 to 2.28)

Quality & Accuracy equivalent to health workers with longer training

- 3 observational studies report lay provider and laboratory staff test results were concordant in nearly all cases
- 2 observational studies comparing lay provider and laboratory staff test results, sensitivity was calculated as 98.0% (95% CI: 96.3-98.9%) and 99.6%, and specificity was calculated as 99.6% (95% CI: 99.4-99.7%) and 100.0%.

Values & Preferences

- General support for lay providers conducting HTS, particularly in RCT & other study measuring preferences among people who had actually undergone HTS with a lay provider.

Cost

- Cost of trained lay providers vary but are generally lower than cost of health providers with longer training.

Trained lay providers can safely and effectively perform HIV testing services using rapid diagnostic tests.
Adding NAT at birth to the existing EID strategy
As EID programmes are further scaled up, every effort should be made to improve uptake of NAT at 4–6 weeks, strengthen retention along the testing-to-treatment cascade, ensure confirmation of NAT positive results with a second sample and ensure that infants who test negative by NAT are retained in care until a final diagnosis is made.

To add NAT at birth, effective linkage to maternal HIV screening at the time of delivery should be ensured and the following steps taken:
- collection of data on performance and feasibility of birth testing during implementation;
- improvement of uptake and retention in the testing-to-treatment cascade;
- active tracking of infants with negative NAT at birth to ensure that they return at six weeks for retesting and cotrimoxazole initiation, and
- retesting of infants who test positive at birth with collection of a second specimen as soon as possible.
ART should be started immediately after the first positive test and can be stopped if the second specimen tests negative.
HIV Testing and Prevention challenges in adolescents

- Lack of family planning services
- Failure to provide prenatal HIV testing
- Failure to provide ART during pregnancy
- Substance abuse
- Routine opt-out HIV testing services
Progress / Achievements

- New options for testing:
  - Self-sampling: you collect your own sample, either of blood or of moisture from your mouth. You send this to a laboratory for analysis. They will make your results available by phone or text a few days later.
  - Self-testing: you collect a sample of blood or of moisture from your mouth. You perform the whole test yourself. After a few minutes, you read and interpret your own test result.
    - Reluctance by USA youth as access to test kits not confidential
    - Thai teens more likely to use if they perceived themselves to be at high risk

- Dedicated youth centres:
  - 12% increase in testing uptake (SA)
Uptake Amongst All Residents in Malawi
Since HIVST Made Available

Highest uptake among adolescents
• 76% in months 1-12
• 74% in months 13-24
• 44% first-time testers
• ~90% returned kits with self-completed questionnaire

Source: Choko et al forthcoming 2015
Linkage

Evidence is limited, but promising$^{1,2}$

- Especially when coupled with a proactive approach (e.g. home-based ART initiation)

- 80-100% of MSM report they would link to further testing and care, if they had a reactive self-test result$^3$

Higher ART among Home Self-test Clusters than Facility-based
MacPherson 2014 (Malawi)

<table>
<thead>
<tr>
<th>Parent Trial Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home-Based Test</td>
</tr>
<tr>
<td>Home Group or Home Option</td>
</tr>
<tr>
<td>(8,194)</td>
</tr>
<tr>
<td>181 Participants initiating ART</td>
</tr>
<tr>
<td>8,013 Participants not initiating ART</td>
</tr>
<tr>
<td>Facility-Based Test</td>
</tr>
<tr>
<td>Facility Group or Facility-Based</td>
</tr>
<tr>
<td>(8,466)</td>
</tr>
<tr>
<td>63 Participants initiating ART</td>
</tr>
<tr>
<td>8,403 Participants not initiating ART</td>
</tr>
</tbody>
</table>

Source: 1 MacPherson 2014; 2 Choko 2014; 3. Figueroa et al. 2015
Linking to care and Retention

- In 2012, only 30% of children who were tested were referred for initiation of antiretroviral therapy.

- A study by Mughasa, in 2014, found only 12% of mother-infant pairs were referred for care in sub-Saharan Africa.

- Retention in care decreases after 6 months.

- Younger children less likely to be retained in care.
## Barriers to Linkage to care of Infants, Children and Adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Clinical setting</th>
<th>Population</th>
<th>Intervention assessed</th>
<th>Barriers identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woldesenbet [7]</td>
<td>South Africa</td>
<td>Immunization service points</td>
<td>Infants presenting for 6 week immunisation</td>
<td>EID at 6 weeks immunization</td>
<td>Poor documentation in Immunisation cards, Mothers’ lack of knowledge of HIV, Fear of discrimination, Lack of provider initiated testing,</td>
</tr>
<tr>
<td>Kranzer [23]</td>
<td>Zimbabwe</td>
<td>Primary care clinics</td>
<td>Children 6–15 years</td>
<td>Provider initiated testing with guardian consent and child assent</td>
<td>Tests were not offered due to lack of staff or kits, Unsuitable guardian present, Children older than 7, clinically well and those accompanied by male or younger guardians were less likely to be offered testing, Male guardians were less likely to consent to testing,</td>
</tr>
<tr>
<td>O’Donnell [24]</td>
<td>Tanzania</td>
<td>Referral hospitals, VCT sites, community</td>
<td>Children 0–17 years</td>
<td>Frequency of testing of children in a high incidence area based on adult HIV status</td>
<td>Younger age group, Caregiver status unknown or negative, Children born prior to parental HIV diagnosis</td>
</tr>
<tr>
<td>Philbin [25]</td>
<td>United States</td>
<td>HIV/AIDS Intervention clinics</td>
<td>Adolescents 12-24 years</td>
<td>Linkage to care and engagement in care of HIV positive adolescents</td>
<td>Male sex, Older age (22-24 year olds less likely), Hispanic race, Sexual identity not documented, Homelessness, Syphilis positive</td>
</tr>
</tbody>
</table>
Improving retention

Studies have shown that retention increases if:

- Facilities with nutritional support (sub-Saharan study)
- Linkages to PLHIVA (Ethiopia)
- Mother-child facilities under one roof (Ethiopia)
- Facilities with Nurse based health care and peer health worker care
Starting ART

The number of children receiving antiretroviral therapy is appallingly low – a mere 24% [22-26%]. Three of four children living with HIV or 76% [74-78%] are not receiving HIV treatment.

Global AIDS Response Reporting (WHO/UNICEF/UNAIDS) and UNAIDS/WHO estimates, 2013*
Early Treatment

- CHER Study

- “Mississippi Baby”

- 18 yr. old French adolescent stays undetectable for twelve years off treatment after early HIV therapy (IAS 2015)

- START trial provides definitive evidence of the benefits of early HIV treatment:
  - Those who started Rx immediately after diagnosis, whilst CD4 counts were high, instead of waiting for CD4 count to drop <350, had significantly lower risk of death and illnesses (IAS 2015)

- Same-day start to antiretroviral treatment leads to faster HIV suppression in San Francisco study (IAS 2015)
Barriers/ Challenges

- Many issues prohibit initiation of treatment for children including lack of training for health workers
- Suboptimal drug formulations, use of non-WHO recommended regimens
- There are fewer antiretroviral drugs available for use by children
- Higher treatment costs.
- Medication supply issues further hamper paediatric treatment.
- Complex formulas complicate pricing and ordering decisions.
Life Cycle of the HIV-1 Virus

Lataillade et al. CROI 2015, Abstract 114LB
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

- Abacavir
  - Not for < 3 mo; available as FDC
- Didanosine
- Emtricitabine
  - Can be used from birth; available as FDC
- Lamivudine
- Stavudine
- Tenofovir Disoproxil Fumarate
  - Recently approved for use > 2yrs; available as FDC
- Zidovudine
Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

- **Efavirenz**
  - Not for < 3yrs; FDC available for >40kg

- **Etravirine**
  - For > 6yrs

- **Nevirapine**

- **Rilpivirine**
  - For use > 18yrs; FDC
  - Clinical trial underway for < 18yr
Protease Inhibitors (PIs)

- **Atazanavir**
  - For use > 3 months > 10 kg; FDC

- **Darunavir**
  - Over 3 yrs and > 10 kg; must be boosted

- **Fosamprenavir**
  - Over 6 mo only and boosted only

- **Indinavir**
  - Generally not recommended; over 12 yrs only

- **Lopinavir/Ritonavir**
  - Pellets and granules now available
    - WHO fact sheet Feb 2016

- **Nelfinavir**
  - Over 2 yrs only

- **Saquinavir**

- **Tipranavir**
  - > 2 yrs: must be boosted
Integrase Inhibitors

- **Raltegravir**
  - From 4 weeks of age
  - Over 3 kg

- **Dolutegravir**
  - Over 12 yrs and > 40kg
  - Paediatric trial for 6-12 yrs P1093: data presented at CROI 2016
  - Trial for 2-6 yrs now underway

- **Elvitegravir**
  - > 18 yrs only
  - With booster
Entry and Fusion Inhibitors

- **Enfuvirtide**
  - Over 6 yrs
  - Twice daily injections

- **Maraviroc**
  - Only if CCR5 tropic
  - > 16 yrs only
  - Paediatric trial underway
Pharmacokinetic Enhancers

- **Cobicistat**
  - Over 18 yrs only
  - FDC

- **Ritonavir**
New formulations/classes

- Pellets
- Sprinkle granules (LPV/rtv; Raltegravir)

- **New formulation of Tenofovir (IAS 2015)**
  - Tenofovir alafenamide (TAF) is a new formulation of tenofovir that reaches higher levels in HIV-infected cells.
  - Less renal and bone mineral toxicities

**New NNRTI:**

**Doravirine (IAS 2015)**

suppresses HIV as well as efavirenz

but with fewer central nervous system side-effects

**New Class:**

**Next-generation maturation inhibitor BMS-955176 shows good antiviral activity in combination with atazanavir (IAS 2015)**
Adherence and viral load suppression

Adherence Level %

COUNTRIES

USA [60] 49
USA [60] 82
Brazil [61] 77
Brazil [61] 92
India [61] 95.3
Nigeria [65] 95
Zimbabwe [66] 57
Zimbabwe [66] 63
Tanzania [67] 85
Tanzania [68] 25
Latin America [69] 98.4
Kenya [70] 96.3
Thailand [72] 83
Thailand [72] 99
Thailand [72] 98

PERCENTAGE %
## Studies on adherence in children and adolescents from several countries

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Age</th>
<th>Methodology or Intervention</th>
<th>Factors promoting adherence/retention/viral load suppression</th>
<th>Barriers/Obstacles to adherence/retention/viral load suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahana [60]</td>
<td>USA</td>
<td>12-26 yrs</td>
<td>Audio computer–assisted self interviews</td>
<td>Perinatally infected youth: consistent care, no drug abuse, non African-American race, younger age. Behaviourally infected youth: Older age, heterosexual, employed, higher education level</td>
<td></td>
</tr>
<tr>
<td>Cruz [61]</td>
<td>Brazil</td>
<td>0-18 yrs</td>
<td>Structured questionnaires to care givers and adolescents</td>
<td>Better quality of life of caregivers; low anxiety scores; low alcohol and drug abuse; short pharmacy visit intervals</td>
<td></td>
</tr>
<tr>
<td>Denison [62]</td>
<td>Zambia</td>
<td>15-18 yrs</td>
<td>Interviews of adolescents and care givers</td>
<td>Family support; youth support groups; wanting to be healthy;</td>
<td>Fear of disclosure; travel away from home; spiritual beliefs; non-disclosure; forgetting</td>
</tr>
<tr>
<td>Seth [63]</td>
<td>India</td>
<td>&lt;15 yrs</td>
<td>Pill count, interviews and questionnaires to child and care giver</td>
<td></td>
<td>Care giver: Multiple care givers; job constraints; death/illness in family; Child: refusal to take medication; asleep; pill load, taste, side effects</td>
</tr>
<tr>
<td>Anigilaje [64]</td>
<td>Nigeria</td>
<td>&lt;15 yrs</td>
<td>Kiddies Club for children and adolescents and care givers</td>
<td>Information received at the club; regular attendance; pill swallowing training; nutritional advice; disclosure; loss of stigma; memory aids via text messages</td>
<td>Financial constraints; long distances to hospitals; transport availability; Lack of disclosure; frequent hospital visits</td>
</tr>
<tr>
<td>Ugwu [65]</td>
<td>Nigeria</td>
<td>5 mo-17 yrs</td>
<td>Self -reporting of 3, 7, 30 day recall</td>
<td>Care –giver had method of remembering, scheduled follow up visits disclosure</td>
<td>Care –giver related; Travelled, ill, forgot, drugs finished, mother primary care giver. Child related: Refused, asleep, vomited, &lt; 5 years of age</td>
</tr>
<tr>
<td>Gross [66]</td>
<td>Zimbabwe</td>
<td>10-19 yrs</td>
<td>Self - completed questionnaire</td>
<td>Presence of care giver during hospital visit; text messaging; group session run by professional</td>
<td></td>
</tr>
</tbody>
</table>

Bobat, Archary et al, 2015
Studies have shown viral load suppression rates to range between 27%-65%

- PIY have better rates than BIY (USA, Brazil)
- children < 2yrs have even poorer rates of suppression (SA)
- VLS improves if community intervention/support (SA)
- Middle income countries had better vls than high income countries

- Currently viral load testing is available to only 25% of the population

- At IAS conference July 2014, the UNAIDS sponsored Diagnostics Access Initiative was launched
  - Companies were challenged to reduce prices for vlt
- In response, in Sept 2014, ROCHE announced sharp decline in price of viral load tests for low and middle income countries
- Now being rolled out in several countries
New Directions in the 2015 Consolidated ARV Guidelines Update

Meg Doherty, MD, PhD, MPH
19 July 2015
WHO Satellite
Vancouver – IAS 2015
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
<table>
<thead>
<tr>
<th>Target population</th>
<th>WHAT IS NEW 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</td>
<td>ART initiation at any CD4</td>
</tr>
<tr>
<td>(10-19 year old)</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>
Programmatic Rationale  Children and Adolescents

- 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
What is new in the 2015 ARV guidelines?

- Treat all (at any CD4) - people living with HIV across all ages

- 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
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• Dr Melissa Lawler
• Mrs. Lee Sewnarain