WHO's Early Release Guidelines
When to Start and PreP

IATT Webinar
October 13, 2015
Contents of this Webinar

1. When to Start in Pregnant and Breast Feeding Women
2. When to Start in Children and Adolescents
3. PreP guidance with a special note on pregnant women
New guidelines recommend universal ART for pregnant and breastfeeding women

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong

**Strong recommendation, moderate-quality evidence**

- In 2010 we had Option A and B
- In 2013 Option A was no longer recommended and we had Option B and B+
- Now lifelong ART is recommended not only for pregnant and breastfeeding women but also for ALL people diagnosed with HIV

Therefore, the new guidelines do not speak of “options” but “universal ART”

- But the rationale behind this isn’t from PMTCT literature....
Temprano is one of the key studies that has driven the recommendation for universal ART

- Multi-centre RCT looking at immediate ART vs. WHO-guided ART
  - Isoniazid preventive therapy (IPT) vs. no IPT
- 9 centres in Abidjan, Côte d’Ivoire
- Well Asymptomatic HIV+ adults with CD4 <800 cells/µL, randomized to 4 arms

<table>
<thead>
<tr>
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<th>WHO-guided ART, no IPT (N=511)</th>
<th>WHO-guided ART, IPT (N=512)</th>
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<tbody>
<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
<td>Immediate ART, no IPT (N=515)</td>
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<tr>
<td>4</td>
<td>Immediate ART, IPT (N=518)</td>
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- Definitions of WHO-guided changed as the guidelines evolved so about half of the patients were enrolled under 2006 guidelines (<200 CD4) and half under the 2010 guidelines (<350 CD4)
Comparing primary outcome, early ART was beneficial in all and also those with CD4 ≥500

Comparing early ART with deferred $p=0.0002$

Comparing early ART with deferred $p=0.027$

The START trial enrolled over 4000 people with CD4>500 at 211 sites in 35 countries

- Europe 33%, South America 25%, Africa 21%, North America 11%, Asia 10%
- Median age 36 years and 25% were women
- Med CD4: 651 (range 503 to 2296) and Med VL: 12,000
- Study design was straightforward – patients randomized to either early start or waiting until CD4 fell below 350
- Trial was closed early by the DSMB because of higher than expected benefit of ART
When looking at the primary outcome of death or severe disease, immediate ART was protective.

Overall there were 42 “events” in the arm and 96 in the deferred arm p=<0.001
No difference in drug toxicities between arms and no evidence of harm caused by ART even in clients with HIV CD4

CIPRA and SMART studies – ART start at CD4 ≤ 350 cells/mm³ led to improvements in HIV mortality, disease progression, & co-morbidities (TB)

Observational studies showed that ART start at CD4 > 350 cells/mm³ improved mortality, disease progression & non-AIDS events

HPTN 052 showed that ART start at CD4 > 500 cells/mm³ markedly reduced transmission and lowered risk of TB

TEMPRANO and START studies show that ART start at CD4 > 500 cells/mm³ improved severe HIV morbidity & disease progression, without an increase in severe adverse events

Temprano/START represent the end of a chain of evidence that has led us to universal ART
So...the “When to Start” recommendations for adults say “treat everyone”

ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count

*strong recommendation, moderate-quality evidence*

As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm³

*strong recommendation, moderate-quality evidence*

For the first time in the history of ARV guidelines...

- ONE recommendation for *everyone*
- erase the distinction between pregnant women and everybody else that has long contributed to poor ART access for women who happen to be pregnant
A community led Global Consultation on the acceptability of ART showed that our clients want this!

- 24 workshops, 8 countries, 8 sub populations, 206 PLHIV, 74 clinicians
- Earlier initiation was deemed *acceptable*, however 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
There are no studies comparing B+ with B but...we do have some data on the effects of stopping ARVs.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Findings from 26 observational studies describing what happens when ARVs stopped</th>
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<tr>
<td><strong>CD4+ decline</strong></td>
<td>Postpartum women who discontinue ART experience CD4 decline, but there is large heterogeneity with findings of studies:</td>
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<td>• Using <strong>CD4 at BASELINE</strong>, CD4 &lt;500 resulted in 6-20% of women reaching treatment threshold within 6 mo of stopping. But if <strong>CD4 was &gt;500, only 1.5%</strong> reached threshold</td>
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<td>• Using <strong>CD4 at TREATMENT STOP</strong>, CD4&gt;550 was associated with 7% of women reaching threshold 18m later, whereas if CD4 was &lt;550 varied from 27-50% women reached threshold at 18m</td>
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<td><strong>Immune activation</strong></td>
<td>In IMPAACT P1025, all inflammatory biomarkers decreased after delivery, but continuation of ART was associated with more rapid decline esp in D-dimer levels.</td>
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<td><strong>Disease progression</strong></td>
<td>Discontinuation when baseline CD4 was &lt;500 resulted in a 2.5-fold higher risk of WHO Stage 2 or 3 clinical events.</td>
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<td><strong>Drug resistance</strong></td>
<td>Paucity of data but in one study, there was a low rate of resistance found in women who stopped NVP-based ART after the period of MTCT risk.</td>
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<td><strong>Retention</strong></td>
<td>Pre-B+, women with high CD4 in Malawi had a 10-fold higher risk of loss to follow up after delivery. In UK 2 out of 3 women who presented at ANC for a second pregnancy were below eligibility threshold.</td>
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Women who stop ART post partum will have *inevitable* progression of disease:

- Clinical events
- CD4 decline
- Inflammatory markers

What is not clear is how *quickly this progression occurs*

- Higher the CD4, the longer it will take
- For all CD4 counts, the TIME TO THRESHOLD in 2015 will be shorter
  – simply because the thresholds are higher!

Looking beyond the science at the programme, *retention for “non-eligible” women is very poor, even in developed countries*. Its hard for the system to catch pre-ART patients before they fall, and a treat all approach can prevent this loss to follow-up...*but what are the downsides?*
B+ (ART for all) will add costs in the short term, but is cost effective compared with option B

- In a CDC led costing exercise total cost (including drugs, diagnostics and service delivery) of maintaining a woman on option B+ for 5 years was estimated to be US$ 2069 on average*
- But a woman off ART also incurs costs of monitoring and follow-up and in time needs ART, so incremental cost of moving from option B to option B+ was relatively low (92 to 605 US$ depending on baseline CD4 count and BF status)
- In modelled cost effectiveness analyses, Option B and B+ are cost-saving or highly cost-effective compared to option A.
- When outcomes such as maternal health, preventing the mother-to-child transmission of HIV in future pregnancies and preventing horizontal transmission are considered, option B+ has been found to be highly cost-effective compared with option B

## Summary

Costs vary but all studies indicate that cost per infection averted is comparable for B and B+.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>CE (DALY/QALY)</th>
<th>CE (Cost per infection averted)</th>
<th>CE (Life Exp.)</th>
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<tbody>
<tr>
<td>Fasawe et al., 2013 (Malawi)</td>
<td>Option A &amp; B</td>
<td>$60/DALY averted (B) $57/DALY averted (B+)</td>
<td>$1,331 (B) $1,265 (B+)</td>
<td>$338 per LYG (B) $455 per LYG (B+)</td>
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<tr>
<td>VanDeusen, et al., Ghana</td>
<td>Option B</td>
<td>$785/QALY gained</td>
<td></td>
<td>$618 per LYG</td>
</tr>
<tr>
<td>Ciaranello et al., Zimbabwe</td>
<td>Option B</td>
<td>(incremental CE over B)</td>
<td></td>
<td>$1370 per LYS</td>
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<tr>
<td>Gopalappa et al., Zambia</td>
<td>Option A</td>
<td></td>
<td>$6,000 - $23,000</td>
<td></td>
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<tr>
<td>Ishikawa, et al., Zambia</td>
<td>Option A &amp; B</td>
<td>$74/QALY gained (B) $132/QALY gained (B+)</td>
<td>$1,023 (B) $1,254 (B+)</td>
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<tr>
<td>Adesina, A. &amp; Alkenbrack, S.</td>
<td>Option B</td>
<td>(average CE across 13 states)*</td>
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<td>US$83,000 (B) US$65,000 (B+)</td>
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# Balance of Risks and Benefits favours universal ART for Pregnant and Breastfeeding Women

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>HARMS</th>
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<td>Preventing transmission in future pregnancies</td>
<td>Additional potential risk of toxicity because of additional time on ART</td>
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<tr>
<td>MTCT if <strong>on ART at conception</strong> is 0.7%*</td>
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<td>Reduced transmission to uninfected partners (hypothesised)</td>
<td>Programmes are seeing high rates of LTFU....this is a systems issue but may have implications for resistance</td>
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<td>Avoid potential downsides to women of stopping and restarting for future pregnancies</td>
<td>Potential risk of loss in transition from MCH delivered ART services to routine ART services</td>
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<td>No need to establish eligibility prior to initiating ART regimen. Makes ART initiation faster and improves PMTCT benefit.</td>
<td>Increased net immediate cost (although like cost effective in the long term)</td>
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<td>Improved maternal mortality &amp; slower disease progression with continuous vs. interrupted ART</td>
<td>Additional potential risk of resistance, especially if women stop ART or are poorly compliant</td>
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<td>Reduces need and cost of CD4 for initial and ongoing eligibility</td>
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<td>Women less likely to drop out of HIV care if they are placed on lifelong ART vs “short term” ARVs</td>
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*Hoffman RM et al. Journal of AIDS March 2010*
For most countries, Universal ART for pregnant women (B+) is already national policy.
New HIV infections among the 21 Global Plan countries dropped below 200,000 in 2014.
ART access for pregnant women has increased with the adoption and implementation of B+.

Aggregate antiretroviral coverage for children (0-14) and pregnant women across 21 Global Plan priority Countries, 2014

Source: UNAIDS Estimates derived from GARPR 2015 data
But when you look at individual countries there is a lot of heterogeneity in terms of coverage.

Antiretroviral Coverage for children (0-14 years) and pregnant women in 21 Global Plan priority countries, 2014

Source: UNAIDS Estimates derived from GARPR 2015 data
And this is reflected in the “percentage reduction” and “new infections in children” data

Number of new HIV infections among children in 2014 and per cent reduction in new infections since 2009

Source: UNAIDS Estimates derived from GARPR 2015 data
Is the policy shift to Universal ART for Pregnant and Breastfeeding women the magic bullet to control MTCT?
New recommendations may be “effective” but can’t work if coverage and retention are poor

100,000 HIV+ mothers

- Attend ANC clinic 90%
- Counseled and tested for HIV, CD4 75%
- Get ARVs (pre, peri, and postnatal) 50%

Access to PMTCT

- 90,000
- 67,500
- 33,750

No PMTCT

- 10,000
- 32,500
- 66,250

1,700 infected (~5% transmission)

26,500 infected (~40% transmission)

~28,200 infections

Slide adapted from P Barker.
Even a “poor” intervention works when there is good coverage and retention

- 100,000 HIV+ mothers
- Attend ANC clinic 95%
- Counseled and tested for HIV, CD4 95%
- Get ARVs (pre, peri, and postnatal) 95%

Access to PMTCT
- 95,000
- 90,250
- 85,738

No PMTCT
- 5,000
- 9,750
- 14,263

8,500 infected (~10% transmission)
- 5700 infected (~40% transmission)
- ~14,200 infections

Slide adapted from P Barker.
Way forwards to eliminate MTCT

• Countries *should* adopt universal ART for PW and BF women
  – Good for mother, good for baby, good for sero-discordant couple
• But the impact of this policy shift is contingent on program performance.
  – Weak health systems need to improve their coverage and retention
  – And to do this will require more money, better systems to track and prevent LTFU, more HCWs and community engagement
• Some areas of implementation focus are emerging
  – Same day Start (ie starting ART on the same day as the test) may result in lack of uptake and high drop off
  – Retesting pos women before ART initiation is essential to ensuring that women who are not truly infected do not get started on ART
  – Postpartum retention is a major problem that could be improved with greater community engagement and facilitated transfer from MCH to ART