Update on Option B+
Successes and Challenges

James McIntyre
Anova Health Institute &
School of Public Health & Family Medicine,
University of Cape Town
“Do not be fooled: People make simple things complex to condone their inertia, and the inertia of those who are living off this epidemic.

Or maybe not inertia, but simple lack of imagination.”

Barcelona, 2002

Joep Lange, 1954 – 2014
Scientist, Activist, Humanitarian
Elimination of perinatal HIV transmission

WE BELIEVE BY 2015, CHILDREN EVERYWHERE CAN BE BORN FREE OF HIV AND THEIR MOTHERS REMAIN ALIVE.

UNAIDS: Global Plan Towards The Elimination Of New HIV Infections Among Children By 2015 And Keeping Their Mothers Alive 2011-2015
Number of new child infections, 21 high burden countries, 2001 - 2013, and projected targets

- 60% reduction from 2001 to 2013
- 65% reduction continuing current trends from 2010
- 90% reduction global plan target of
From evidence to policy
## Evolution of WHO PMTCT ARV Recommendations

<table>
<thead>
<tr>
<th>Year</th>
<th>PMTCT</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>4 weeks AZT; AZT+ 3TC, or SD NVP</td>
<td>No recommendation</td>
</tr>
<tr>
<td>2004</td>
<td>AZT from 28 wks + SD NVP</td>
<td>CD4 &lt;200</td>
</tr>
<tr>
<td>2006</td>
<td>AZT from 28wks + sdNVP +AZT/3TC 7days</td>
<td>CD4 &lt;200</td>
</tr>
<tr>
<td>2010</td>
<td>Option A (AZT +infant NVP)</td>
<td>CD4 &lt;350</td>
</tr>
<tr>
<td>2013</td>
<td>Option B (triple ARVs)</td>
<td>CD4 &lt;500</td>
</tr>
</tbody>
</table>

Move towards: more effective ARV drugs, extending coverage throughout MTCT risk period, ART for the mother’s health, increased consideration of operational and program implementation issues

Adapted from Shaffer, WHO 2013
“We propose to offer all HIV-infected pregnant women lifelong ART. This approach is not completely new, but rather is a more feasible alternative to WHO’s proposed option B, which we call option B+.”

Lancet 2011; 378: 282–84
The potential of Option B and B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons.

Options B and specifically B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons.

• Options B and B+ offer significant operational advantages over Option A.
• There are added clinical benefits of Options B and B+.
• The costs averted by Option B exceed the spending it requires over Option A. The additional benefits of Option B+ may exceed its associated costs.

BLC & UNICEF 2012
The potential of Option B and B+

Potential key benefits of either Option B or Option B+ include:

• Ensuring that all ‘ART-eligible’ pregnant women receive triple antiretrovirals for their own health as well as to prevent MTCT,
• Preventing MTCT in future pregnancies,
• Avoiding the risks of starting and stopping antiretrovirals,
• Potential health benefits of early initiation of ART
• A major simplification of programmes, algorithms, drug regimen (a once-daily fixed-dose combination) and messages.
Expressed concerns about Option B+

"The business case, which supports use of Option B+ in resource-limited settings, does not fully address four critical considerations: ethics, medical safety and benefits, programme feasibility, and economic concerns."

Coutsoudis, Goga, Desmond, Barron, Black & Coovadia. 2013
Expressed concerns about Option B+

“Not a single comparative trial or observational cohort has been conducted on its ability to improve long term maternal health, to reach an acceptable adherence rate, to prevent HIV transmission to children (including in subsequent pregnancies), or to offer measurable wellbeing to the community.”

Van De Perre, Tylleskär, Delfraissy & Nagot, BMJ 2013
WHO Consolidated Guideline 2013:

- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART.

- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment.

- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased.
More Research is Needed to Support the WHO 2013 Recommendations

The WHO 2013 Consolidated Guidelines acknowledge the need for additional research “to support the recommendations, inform programmatic decisions and to promote optimal implementation”:

**ARV toxicity surveillance:**
- safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in low resource settings.

**Maternal and child health outcomes:**
- better define the long-term outcomes for both mother-to-child transmission at the end of breastfeeding and maternal health.

**Adherence and retention:**
- how to optimize acceptability, adherence and retention on ART in pregnant and breastfeeding women.
Option B+ : defining “success”

**success**
/sekˈses/

*noun*

1. the accomplishment of an aim or purpose.
   "the president had some success in restoring confidence"
   synonyms: favourable outcome, successfulness, favourable result, successful
   outcome, positive result, victory, triumph

2. archaic
   the good or bad outcome of an undertaking.
   "the good or ill success of their maritime enterprises"
“It also remains to be determined whether this approach improves ARV adherence, retention of mothers and children across the PMTCT cascade, and whether it is effective at keeping mothers healthy and protecting infants from acquiring HIV infection”

Abrams & Myer, JAIDS 2013
Defining success: two rules..

“IN GOD WE TRUST; ALL OTHERS MUST BRING DATA.”
- W. EDWARDS DEMING

If we have data, let’s look at data. If all we have are opinions, let’s go with mine.

Jim Barksdale
NETSCAPE
Option B+ : defining “success” by opinion

“Option B+ has the potential to **vastly improve the health outcomes** of HIV+ mothers and their infants”

UNICEF spokesperson

“Option B+ offers **no advantage to PMTCT** and there are social hazards associated with privileging pregnant woman for treatment over men and non-pregnant women”

Coutsoudis et al, Lancet 2013

“Option B+ is a triumph of marketing over data”

Anonymous Activist, 2014
Option B+ : defining “success” by press report

Health: Option B+ A Better Way to Prevent Mother to Child Transmission

AIDS Activists Commend, Criticize Uganda's Option B+ Implementation

From Henry J. Kaiser Family Foundation

HIV Activist Protest Mandatory Implementation of Option B Plus

ARV Shortages Hit Mozambique’s HIV Treatment Programme

By Amos Zacarias
Defining success by adoption of policy:

Uganda adopts EMTCT intervention Option B+

Ethiopia Launches Option B+

Zambia Adopts Option B+

Implementing Option B+ in Lesotho
Defining success by adoption of policy:

PMTCT Regimen policies in the priority countries.

<table>
<thead>
<tr>
<th>Mixed</th>
<th>B</th>
<th>B+</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (A &amp; B)</td>
<td>Botswana</td>
<td>Angola</td>
</tr>
<tr>
<td>Kenya (A &amp; B)</td>
<td>Chad</td>
<td>Burundi</td>
</tr>
<tr>
<td>Nigeria (A &amp; B)</td>
<td>Cote d’Ivoire</td>
<td>Cameroon</td>
</tr>
<tr>
<td>Swaziland (A &amp; B+)</td>
<td>Ghana</td>
<td>DRC</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>Ethiopia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lesotho</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malawi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mozambique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Namibia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tanzania</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uganda</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zambia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>
Defining success by WHO’s stated benefits:

...providing an optimized, fixed-dose combination first-line ART regimen...to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits, including the following

- Ease of implementation.
- Harmonized regimens
- Increased coverage of ART.
- Vertical transmission benefit.
- Maternal health benefit.
- Acceptability.
- Sexual prevention benefit.
Ease of implementation

• Implementation of Option B+ and change from Option A has required major investments in health system preparation.

• This is reflected in the delay in implementation in many countries

• “Simplification” of drug regimen is only one part of implementation success: procurement and supply chain management remain major challenges

• Little attention has been paid to the provision of alternate regimen (Option A) if women decline ART
Ease of implementation

- Rapid increases in numbers of women receiving ART in pregnancy signal success at facility level.
- Programmes need to evolve to ensure better tracking and monitoring of both mothers and children

“Great promise but some early caution”
(Shaffer, Abrams & Becquet, 2014)
Harmonized regimens

“The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults.”
Worryingly, ARV shortages threaten Mozambique’s plan to scale up Option B+, the treatment option recommended by WHO for HIV positive mothers.

In 2013, nearly 85,000 HIV positive pregnant women were given ARVs to prevent transmission to their babies. Of these, half were enrolled in Option B+. This means they must get a monthly supply of 30 pills for the rest of their lives.

“It is crucial to keep these women on treatment but it is not easy due to long distances between clinics and communities,” said Guillermo Marquez, HIV specialist with the UNICEF in Maputo.
More evidence for the safety of efavirenz in early pregnancy

An updated systematic review and meta-analysis of the safety of efavirenz in the first trimester of pregnancy:

• 23 studies included: birth outcomes of 2,026 live births among women exposed to efavirenz during the first trimester of pregnancy.

• 44 congenital anomalies were reported, giving a pooled proportion of 1.63% [(95% CI) 0.78-2.48], with only one neural tube defect.

• No difference in relative risks of congenital anomalies comparing women exposed to efavirenz and non-efavirenz-based antiretroviral regimens.

• The incidence of neural tube defects was low, 0.05% (95% CI <0.01-0.28), and similar to incidence in the general population.

“This updated analysis found no evidence of an increased risk of overall or central nervous system congenital anomalies associated with first-trimester exposure to efavirenz. Continued birth outcomes prospective surveillance is warranted”
Low prevalence of renal dysfunction in HIV-infected pregnant women

• Few data on the prevalence of pre-existing renal disease in HIV-infected pregnant women and in turn, the potential related risks of tenofovir use are not well understood

• In a study in Gugulethu, Cape Town, fewer than 1% of pregnant women had moderate renal dysfunction before ART initiation, with no instances of severe dysfunction observed, compared to 7% moderate or severe renal dysfunction in non-pregnant women or men (P < 0.001).

• The risks associated with initiating tenofovir immediately in pregnant women before reviewing serum creatinine results may be limited, and the benefits of rapid ART initiation in pregnancy may outweigh possible risks of nephrotoxicity

Myer et al, Trop Med Int Health, 2013
Harmonized regimens

Challenges remain:

- Limited safety data for efavirenz and tenofovir in pregnancy (mothers and infants) especially in populations with underlying malnutrition/comorbidities

- Conflicting data on triple ARV and preterm delivery

- Little data on need to substitute, mental health and depression issues in pregnancy & postpartum
Increased coverage of ART

“This ensures that immunocompromised women who do not have access to CD4 testing receive appropriate ART without delay.”

• Initial data demonstrates rapid increase in ART access with introduction of Option B and B+

• This is balanced by concerns about the high numbers of women with initiation only in late pregnancy and postpartum (with no antepartum cover), and outcomes when women decline ART
Improved ART access and uptake among pregnant and breastfeeding women, Malawi
Increase in ART Access for Pregnant Women Following Implementation of Option B+ in Malawi

- The number of women initiated on ART increased from 1,257 in 2011 (prior to Option B+) to 10,663 in 2012 (one year after implementation)—a 748% increase.

- 77% of pregnant and breastfeeding women remained on Option B+ twelve months after initiation, similar to the 12-month ART retention rate among adults who initiated ART (80%)

- 4,839 health workers were trained to provide lifelong ART to pregnant women.

- The number of health centers providing ART to pregnant women living with HIV more than doubled from 303 sites in June 2011 to 641 in September 2012.

- Pregnant women starting ART represented 5% of all new ART initiations in the 3rd quarter of 2011, increasing to 35% of all new ART initiations in the 3rd quarter of 2012.

MMWR, March 1, 2013
Improved ART access and uptake among pregnant and breastfeeding women, Malawi

In the initial 9 months: 41% of women only started ART during the breastfeeding period, and in the next six months 25% of women only started during the breastfeeding period.
Malawi programme data

A retrospective cohort study within a demographic surveillance system in northern Malawi.

- 86% had tested for HIV before the pregnancy, 90% tested or re-tested at the ANC visit, and <1% had never tested.

- At first ANC attendance 30% of HIV-positive pregnant women were already on ART

- 43% of HIV-positive pregnant women not already on ART did not start ART during pregnancy or delivery, and at least 20% of HIV exposed babies did not receive nevirapine.

Price et al, STI. 2014
Ugandan experience

Uganda - Week ending 2014-07-13 (W28)

### Weekly Reporting Rate
- **88%**
- 1475 of 1677 reports received.

### % of Women Tested for HIV
- **100%**
- 24060 ANC 1st Visits

### % Women Initiated on Option B+
- **79%**
- 720 Initiated on ART

### Stockouts and Missed Appointments
- Facilities without ARVs: 1% (21)
- Facilities without Test Kits: 3% (58)
- Number Missed Appointments: 895

### EID Testing for July 2014
- Number of EID tests: 1498
- Number of positive EID tests: 82
- Proportion testing positive: 5.5%

*EID data is a cumulative monthly total (and not weekly). The EID Numbers include data up to 2014-07-11.*

http://reports.dhis2sms.ug
The challenge of retention in care

Poor retention in care or adherence to treatment during the postpartum period, may present a threat to both HIV-infected mothers on ART and their infants
The challenge of retention in care

- Retention in care, from the date of ART initiation up to 6 months, for women in the Malawi Option B+ program.

- Analysed nationwide facility-level data on women who started ART at 540 facilities (n = 21,939), as well as individual-level data on patients who started ART at 19 large facilities (n = 11,534).

- 17% lost to follow-up 6 months after ART initiation

- Most losses occurred in the first 3 months of therapy

- Loss to Follow up varied considerably between facilities, ranging from 0 to 58%. Higher loss to follow up at large facilities

Tenthani et al, AIDS 2014
The challenge of retention in care

Associated with loss to follow up:

• Compared to women who initiated ART for their own health, women who started ART to prevent MTCT during pregnancy were **five times more likely never to return to the clinic** after they initiated ART [odds ratio (OR) 5.0, (95% CI) 4.2–6.1].

• More than 1/3 of all pregnant Option B+ patients initiated ART on the day of diagnosis, and members of this group were almost **twice as likely never to return to the facilities** after the initial visit as pregnant Option B+ patients who started later

• Option B+ patients who started therapy while breastfeeding were **twice as likely to miss their first follow-up visit** (OR 2.2, 95%CI 1.8–2.8).

Tenthani et al, AIDS 2014
Vertical transmission benefit

“Provides coverage with ART to maximize the prevention of infant infections”

- Transmission benefit is clear compared to no ART
- Less data on any superiority over Option A or Option B
- Transmission benefit may be a more long term success story: as more women are on ART prior to future pregnancies.
Vertical transmission benefit

Ugandan study comparing early transmission rates with Option B+ with historical controls:

- There were no significant differences in early HIV infection rates among HIV exposed infants whose mothers received option B+ compared to those who had earlier received option A.

Nabweteme-Mugerwa et al, CROI 2014, P-T8
Maternal health benefit

“Will delay disease progression over the course of treatment”

- No evidence to date on maternal health benefit
- Anticipated advantages of early treatment will depend on adherence post partum
- Evidence to date reflects pregnancy and first few months post partum: data on early lifelong treatment, need for second line treatment and resistance issues not yet available
Challenge of adherence in pregnancy and postpartum

Adherence among pregnant and postpartum women not optimal

**Pregnancy stage**
- Antepartum: 75.7% (71.5, 79.7)
- Postpartum: 53.0% (32.8, 72.7)

**Antiretroviral therapy**
- ZDV: 79.0% (70.2, 86.6)
- sdNVP: 78.6% (73.5, 83.4)
- cART: 63.5% (55.8, 70.8)

**Adherence measure**
- Pharmacy: 73.0% (20.4, 70.4)
- Pill count: 73.0% (60.7, 83.7)
- Self-report: 72.2% (70.2, 78.1)
- Blood drug concentration: 72.6% (66.6, 78.2)

Nachega, AIDS 2012

Abrams 2013
Adherence issues

Factors most commonly associated with low adherence to ARV for PMTCT:

- giving birth at home,
- quality and timing of HIV testing and counselling
- few antenatal (ANC) visits,
- financial logistical challenges,
- lack of patient confidentiality

- fear of stigma,
- lack of male involvement,
- fear of partner's reaction to disclosure, women's fear of violence.

Columbini, AIDS Care, 2013
Detectable Viremia Among HIV+ Pregnant Women on ART at first ANC, South Africa

- 364 HIV+ pregnant women reported being on ART at 1st ANC visit, 4/2013-1/2014 (prior to B+); median duration ART 2.7 yrs; assessed viral load first ANC visit.
- TDF/3TC/EFV (50%) or NVP (18%); 12% 2nd line PI

24% of women entering PMTCT already on ART had detectable viremia, 13% >1000 c/mL.
Possible resistance benefits?

- Previous evidence of high rates of NNRTI resistance following sdNVP in “Option A”, moderated by use of “tail” cover

- Long half life of EFV: in planned interruption trials in adults with AZT/3TC/EFV: NNRTI mutations 12.5% - 20.7% without tail, 10% - 15% with tail
  

- Little data on resistance risk after stopping ARV at end of breastfeeding in “Option B” – possibly less concerning, due to viral suppression and nature of drugs in FDC

- No viral load monitoring to determine if woman is suppressed at time of interruption with Option B
Possible resistance benefits of option B+?

Several factors may increase resistance risk, even with Option B+:

• Suboptimal adherence during pregnancy and breastfeeding can jeopardize individual health outcomes and lead to increased transmission of drug resistant HIV

• Health system challenges (drug stockouts, transfers between antenatal and ART services, systems unprepared to deliver lifelong ART)

• Disengagement from care, maternal travel, unwilling to continue ART postpartum

Adapted from Abrams, 2014
Long terminal half-lives of TDF and FTC may protect against NNRTI resistance

3TC-TP, lamivudine triphosphate; FTC-TP, emtricitabine triphosphate, efavirenz (plasma); TFV-DP, tenofovir diphosphate; ZDV-TP, zidovudine triphosphate.

Adapted from Abrams, Berlin 2014; Lamorde, Shapiro, Berger, Black, WHO Guidelines Meeting, 2013, informed by Jackson, JAIDS 2013
Acceptability.

I am a pregnant woman living with HIV.
I face these issues.

- I live far away from a clinic and have not been tested for HIV.
- My husband will beat me and leave me if he knows I have HIV.
- I am scared that my baby will be born with HIV.
- My husband will beat me and leave me if he knows I have HIV.
- Lines are long at the clinic and nobody can care for my children, so I cannot always go.
- When I take my child to the clinic, the services are poor.
- I am afraid that my other children also have HIV.
- My health worker insisted I have an abortion.
- I just want my baby to be born healthy.
- If I talk with my child about HIV, I will have to talk about sex and I am not ready.
- There is no privacy when I visit the clinic, I feel exposed.
- I would like family planning advice, but there are no services near me.
Acceptability

“What they wanted was to give birth; nothing else”

Challenges to postpartum retention in care under Option B+ at a clinic in Johannesburg

Postpartum women attending HIV care perceived that barriers to HIV-care post-delivery for other women included:

- the belief that mothers care more about the baby’s health than their own (29.2%)
- that women were “ignorant” or “irresponsible” (16.7%)
- negative clinic staff treatment (12.5%)
- denial or lack of disclosure of HIV status (10.4%)

Clouse et al, JAIDS 2014
Acceptability

“What they wanted was to give birth; nothing else”

Experienced barriers included
- lack of money (18.0%),
- work conflict (6.0%)
- negative staff treatment (6.0%).

In focus group discussions, three main themes emerged:
- conflict with work commitment,
- negative treatment from health care workers and
- lack of disclosure related to stigma.

Clouse et al, JAIDS 2014
Sexual prevention benefit

“ART will reduce sexual transmission of HIV to sexual partners “

• Scientific plausibility: no data yet

• Reduction in sexual transmission assumes retention on treatment and good adherence

• Development of resistance in non-adherent women may result in the loss of benefits for PMTCT and sexual transmission
Cost-effectiveness

• Costs are driven more by health systems than drug cost
• Models suggest cost-effectiveness of Option B+ in African settings
• Data indicate incremental cost effectiveness ratios of $455 to $1370 per year of life saved
• Real data needed to validate models

Understand the challenges for Option B+
Individual Level Challenges

• Reluctance by women to disclose their HIV status, or to take ARV

• Perceptions that postpartum ARV is no longer required

• Need for targeted and effective health education to overcome fear and support treatment

• If women decline triple ARV: need for alternative regimens and support for these

• Interventions needed to promote retention, such as motivating text messages
Community Level Challenges

• Community education and stigma reduction interventions are still needed

• The need for male involvement remains unaddressed in most settings.

• Alternative community delivery systems, peer support interventions and intensive messaging are all still needed.
Health system challenges:

- Significant additional resources required
- Rapid increase in trained staff and task shifting needed
- Health service planning is required
Health system challenges:

• Supply chain strengthening is essential: Drug costs, sustainability of supply and treatment equity concern

• Service quality must be sustained

• Innovative approaches are needed: community care, alternative delivery, adherence clubs

• More integration of PMTCT, ART and antenatal care needed
Monitoring and evaluation challenges:

- Need to track mothers and babies
- Need to understand disengagement from care: moving between services, vs. loss to follow up
- Pharmacovigilance is still essential
- Resistance monitoring is needed
Research Challenges

Ongoing need for additional research “to support the recommendations, inform programmatic decisions and to promote optimal implementation”

- ARV toxicity surveillance
- Maternal and child health outcomes
- Adherence and retention:
- Pharmacovigilance & resistance
- Health systems
Research Challenges

• A diminishing PMTCT research field?

• Abstracts tagged “PMTCT”:

  224  122

Towards end of enrolment for primary antenatal objective by October 2014

• Increasing need for “implementation science”
Elimination of perinatal HIV transmission

• The elimination of perinatal HIV transmission requires commitment to doing the things that we know work

• It requires access to appropriate care, adequate laboratories, affordable and available drugs and well-trained health workers

• Option B+ is an opportunity, not yet a solution
“Try not. DO or DO NOT. There is no try.”

~ Yoda
ZERO

530

days left to achieve zero new vertical transmission by 2015
Acknowledgements......

With thanks to:

• Elaine Abrams
• Lynne Mofenson
• Coceka Mnyani
• Landon Myer

For generously sharing slides and thoughts, and many other researchers whose work has been mentioned.

6th International Workshop on HIV Pediatrics