Medical and Ethical considerations/issues around Option B+

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Benefits of B+

1. Easier implementation
2. Possibly lower horizontal transmission
3. Possibly long term cost effective

Suitable for countries with very limited resources (eg no access to CD4 tests) and especially with high fertility rate – eg Malawi.

Benefits of B+

1. Easier implementation
2. Possibly lower horizontal transmission
3. Possibly long term cost effective

I will argue that currently insufficient evidence for the other benefits of B+:

- **Decreased PMTCT**
- **Improved Maternal Health balanced against increased risk of side effects and resistance to ARVs**

Finally I will discuss the ethical considerations of implementing B+

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Medical considerations – do we get better PMTCT with B+?

For current pregnancy:
No evidence for efficacy of B (and therefore B +) over A throughout pregnancy & postpartum

- Evidence that A=B *in utero*/intrapartum for women with CD4>350 (*de Vincenzi*)
- BAN-Malawi – no diffs in 6 months postpartum option B vs option A for PMTCT

Medical considerations – do we get better PMTCT with B+?

Furthermore – concentrating on strengthening A by increasing timely CD4 would ensure that we reach high risk mums with CD4 < 350 (Kuhn et al, AIDS 2010 – estimated 88% of transmission occurs in this high risk group). Therefore B or B+ is not likely to add much additional benefit for PMTCT

Medical considerations – do we get better maternal health with B+?

For adults (including mothers) unequivocal evidence that ART improves health outcomes when initiated at CD4 ≤350

Non-pregnant adult data for starting ART at CD4>350 **are not clear**
Likely benefits for CD4 350 to ±500 (Cohen, *NEJM* 2011)
Benefits unclear for CD4 > ±500

Can we generalize data from non-pregnant women & men to pregnant women?

Medical considerations – do we get better maternal health with B+?

We do have evidence of benefit to maternal health in mothers with CD4 < 350 - these are the very same women who would be covered by ARVs in Option A.

(Kuhn L et al, AIDS 2010, showed that the mothers most at risk for mortality were those with CD4 < 350 – 92% risk)

Should we implement a costly programme based on inconclusive evidence on maternal health especially since there are other ways to keep a mother healthy – "wellness concept" – nutrition, psychosocial support etc.

Balancing maternal health with side effects – is it worth the side effects in woman with CD4 > 350?

With B/B+ the side effects of ARVs could be considerable after prolonged use.

limited data on TDF and its effect on renal function and bone density – can we afford the costs of managing these side effects?

ARV Drugs in Pregnancy and Adverse Pregnancy Outcome

- Botswana (*Chen JY et al. 19th CROI, Seattle, WA, March 2012 (Abs 1028)*

  32,113 births; 9,504 (29.6%) women HIV-infected, 9,149 (97%) with known data ARV in pregnancy.

  Among HIV-infected, those on ARVs, especially if started prior to birth, significantly associated with preterm delivery, SGA and stillbirth compared to AZT (economic; quality of life; and health system costs of prematurity and low birth weight cannot be ignored).

Outcome	Continued ART (pre-pregnancy) (N=2,189)	Started ART (N=1,101)	AZT (N=4,625)
Preterm	26.5%	19.8%	14.2%
SGA	26.1%	21.5%	14.2%
Stillbirth	6.3%	4.7%	1.7%

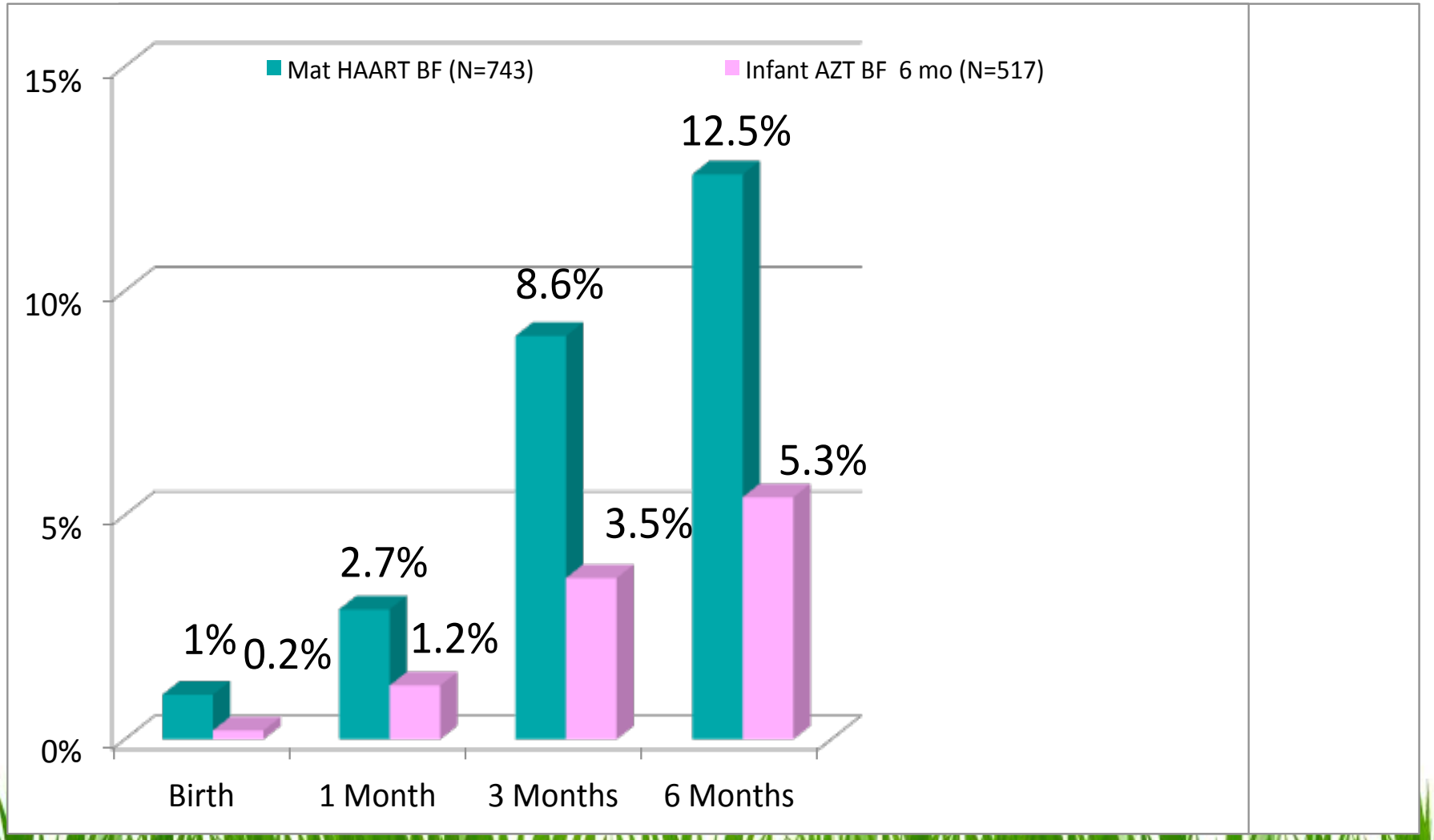
Balancing infant health/side effects – are these disadvantages outweighed by benefits?

Possible drug toxicity from ingestion of drugs through breastmilk with B and B+

Possible bone density problems TDF in breastmilk

Higher Rates of Anemia in Infants of Mothers on Triple Drug Prophylaxis vs AZT in Mashi Study

Dryden-Peterson S et al. JAIDS. 2011; 56:428-36



ARV resistance with option B+

With option A lower risk of maternal resistance – AZT low resistance profile and Truvada cover is provided to mitigate against possible NVP resistance

However ARV resistance a major concern for option B+ especially if adherence is poor. Potential for very high levels of drug resistance as well as probability of transmitted resistance – major implications for general population.

Financial and health system costs of early introduction of 2nd and 3rd line treatment need to be seriously considered.

Risk of ARV resistance in infants

With B+/B any resistance that may develop will be multi-drug resistance (option A only single drug resistance).

Furthermore, with option A because of long half-life of nevirapine it “allows” infant to miss some doses while maintaining adequate drug levels thus providing an adherence “safety net”.

Ethical considerations: even if a country can afford the financial costs is it ethical?

Should we be putting scarce financial resources into a programme with insufficient evidence while other possibly more important programmes will be compromised – what are the opportunity costs to B+?

What other important programmes are being compromised eg: *behaviour change programmes; family planning; empowering of women; etc which could impact on earlier steps of PMTCT cascade with possible greater benefits than simply introducing drugs.* (Preventing unintended pregnancies in HIV+ women is the most efficacious & efficient form of PMTCT)

Ethical Issues – are we disempowering mothers- paternalistic/ condescending attitude??

What message are we giving to mothers?? Are we perhaps implying:

“ we know that you are so hopeless there is no way you can take care of your health and you are so highly infectious that you are just going to be going around infecting everybody therefore we are going to do this for you and strongly encourage/coerce you to take a tablet every day”.

Is a costly drug policy the only way to reduce transmission to partners? What about behavioural interventions which are more empowering and will have an impact on other aspects of the mother’s life and not only on HIV.

Ethical considerations – have we checked if taking ARVs for life in well mothers, is acceptable?

- Meta-analysis of 48 studies of ART adherence in pregnant and postpartum women showed postpartum adherence only 50% (Nachega J et al)
- HIV+ pregnant women often clinically well → if child tests HIV-negative, motivation for lifelong ART may decline compared to other patients (Stinson AJAR 2012)

Ethical considerations – have we checked if taking ARVs for life, in well mothers is acceptable?

Results of FGDs in Uganda and Malawi, Nov 2012, conducted by GNP+ and ICW:

- Overall consensus of insufficient dialogue with women before implementation – lack of information.
- Overall most important benefit stated was being able to breastfeed longer – highlights the lack of accurate information since being able to breastfeed longer is one of the benefits of A and B as well.
- In Malawi, strong consensus that B+ was presented as the only option, to the point of coercion.

Ethical Considerations - Equity issues

B+ may lead to inequities in society – putting so much effort into coverage with ARVs, for mothers with CD4 > 350 who probably don't need them, while many others adults with CD4 < 350 are not being prioritised for treatment.

Ethical Considerations - other issues

If mothers are not given sufficient accurate information, and if it is not presented to them in a respectful way they will probably not be convinced of the need to be on treatment for life.

Could we then be left with the same situation as we had with formula milk? Will mothers be selling their ARVs?

You may think the grass is greener on the other side, but if you take the time to water your own grass it would be just as green.....

Outstanding Research – awaiting results of PROMISE A vs B vs B+ (short term)

These results are vital- several African countries committed themselves to a large expensive study and thousands of mothers have consented to be in the study, is it ethical to ignore this and just move ahead without waiting for the results?

Special independent ethical review panel set up to decide whether the PROMISE study should be discontinued given that so many countries were moving ahead with option B or B+ - Panel recommended continuing since the questions being asked have still not be answered.

Outstanding Research – for countries already implementing B or B+ - we need M & E research.

- Pharmacovigilance for side effects especially after prolonged periods
- Registers of birth defects
- Registers of adverse birth outcome
- Adherence and Retention in Care
- Surveillance for HIV resistance among mothers and among infants who become infected
- Impact of Option B/B+ on the ability of the country program to serve all adults in need of treatment

Outstanding Research – new experimental research needed – within country comparison of B vs B+:

- Progression to AIDS after 5, 10 years
- Balanced against cumulative side effects 5, 10 yrs
- Cost effectiveness analysis
- Development of ARV resistance in mothers as well as in infants who become infected
- Side effects in infants
- Acceptability to mothers, their families and community.
- Models of retention in care

Outstanding Research – new experimental research needed – within country comparison of B vs B+:

- impact of Options B versus B+ on horizontal HIV transmission and community HIV incidence
- Infant health in B vs B+ (hypothesis that maternal health will be improved therefore infant health should be improved)
- Quality of life in B vs B+ - 5 and 10 years after randomisation