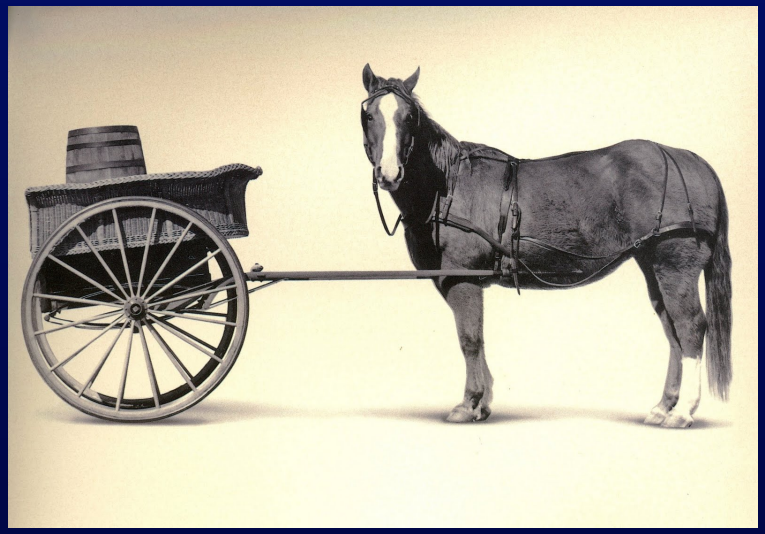
Scientific and Programmatic Advances in PMTCT: To B or to B+?



Roger Shapiro, MD, MPH
Associate Professor of Medicine
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PMTCT 1994-2006

- ACTG 076: ZDV reduced MTCT by ~ 67%
- HIVNET 012: sdNVP reduced MTCT by ~ 50%
- WITS and other US / European data: Viral load reduction from HAART extremely effective at PMTCT

The New England Journal of Medicine

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Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Moye, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D., for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*

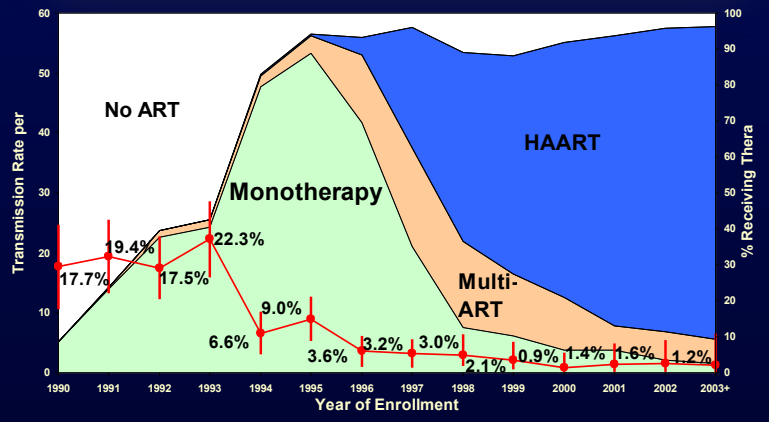
THE LANCET

Volume 354, Issue 9181, 4 September 1999, Pages 795–802

Articles

Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial

Laura A Guay, Philippa Musoke, Thomas Fleming, Danstan Bagenda, Melissa Allen, Clemensia Nakabiito, Joseph Sherman, Paul Bakaki, Constance Ducar, Martina Deseyve, Lynda Emel, Mark Mirochnick, Mary Glenn Fowler, Lynne Mofenson, Paolo Miotti, Kevin Dransfield, Dorothy Bray, Francis Mmiro, J Brooks Jackson



2006 WHO Guidelines

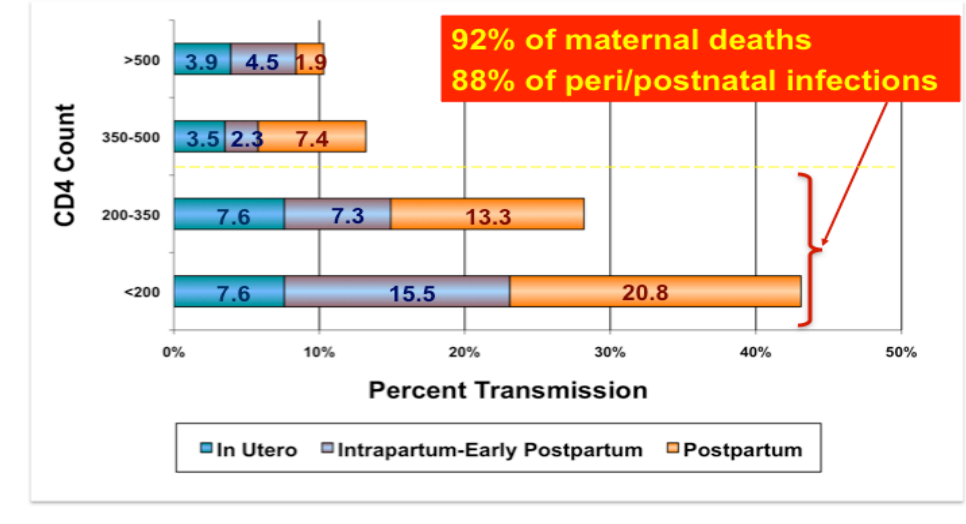
- Summarized scientific data for each clinical scenario, and endorsed many options:
  - *AZT alone*
  - *AZT together with 3TC*
  - *NVP alone (single dose for mother and infant)*
  - *AZT + Sd-NVP for mother and/or infant*
  - *AZT + 3TC plus Sd-NVP for mother and/or infant*
  - *triple-ARV combination regimens*
- ART recommended according to national guidelines
- The “default option” of using sdNVP alone was endorsed for resource-limited settings
  - allowed countries to choose sdNVP as easiest / cheapest option
- No prophylaxis option for BF

2006 WHO PMTCT Guidelines
"just do what you can"

(WHO not leading, countries not following)

Advances in PMTCT from 2006-2009

- HAART became more feasible as a PMTCT strategy for the developing world
  - Interest in reconciling developing/developed world guidelines where possible, especially for treatment
  - Movement toward CD4 treatment threshold < 350 (2006 WHO guidelines: "consider treatment" 200-350)
    - if ~ half of HIV+ pregnant women potentially treatment eligible, opened door to meaningful PMTCT impact:



Kuhn, AIDS 2010

Advances in PMTCT from 2006-2009

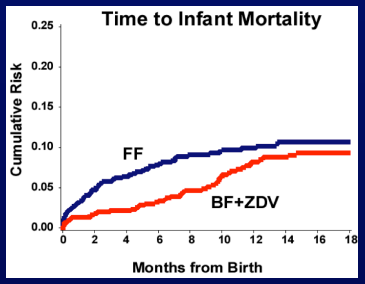
- Stronger evidence that lack of breastfeeding or early weaning unsafe

The NEW ENGLAND JOURNAL *of* MEDICINE

Effects of Early, Abrupt Weaning for HIV-free Survival of Children in Zambia

Breastfeeding Plus Infant Zidovudine Prophylaxis for 6 Months vs Formula Feeding Plus Infant Zidovudine for 1 Month to Reduce Mother-to-Child HIV Transmission in Botswana

A Randomized Trial: The Mashi Study



Hospitalization and Mortality Among Primarily Nonbreastfed Children During a Large Outbreak of Diarrhea and Malnutrition in Botswana, 2006

Early Weaning of HIV-Exposed Uninfected Infants and Risk of Serious Gastroenteritis: Findings from Two Perinatal HIV Prevention Trials in Kampala, Uganda

Breastfeeding, Mother-to-Child HIV Transmission, and Mortality Among Infants Born to HIV-Infected Women on Highly Active Antiretroviral Therapy in Rural Uganda

Frequency of Gastroenteritis and Gastroenteritis-Associated Mortality With Early Weaning in HIV-1–Uninfected Children Born to HIV-Infected Women in Malawi

- First data for use of either maternal HAART or infant NVP to reduce breastfeeding MTCT

Maternal or Infant Antiretroviral Drugs to Reduce HIV-1 Transmission

The NEW ENGLAND JOURNAL *of* MEDICINE

Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana

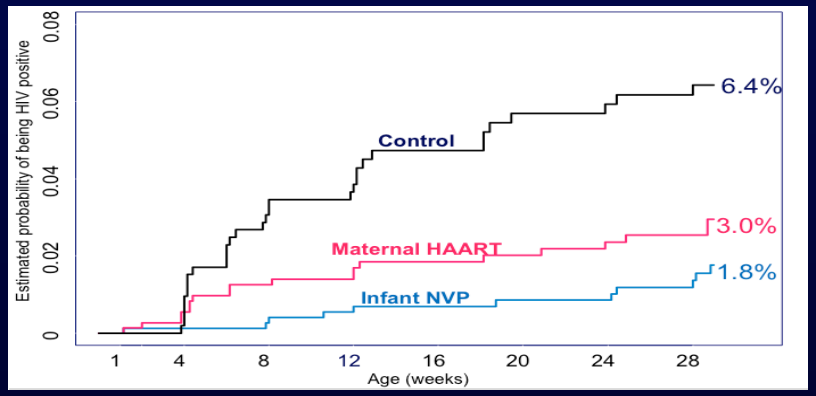


Table 2. Timing and Characteristics of Transmission of HIV-1 from Mothers to Infants.*

Mother–Infant Pair No.	Study Group	Mothers: Duration of HAART at First Positive DNA PCR	Mothers: Baseline CD4+ Count	Mothers: Baseline HIV-1 RNA	Mothers: Plasma HIV-1 RNA at Delivery	Mothers: Plasma HIV-1 RNA at 1 and 3 Mo	Mothers: Breast-Milk HIV-1 RNA at 1 and 3 Mo	Mothers: HAART Adherence Issues†	Infants: Age at First Positive DNA PCR	Infants: Gestational Age at Delivery	Infants: Status at 6 Mo
		wk	cells/mm³	copies per milliliter					day	wk	
1	NRTI	7.0	237	80,300	<50	NA	NA	No	1	39	Alive
2‡	NRTI	3.4	317	>750,000	None§	NA	NA	Yes	1	30	Dead
3	NRTI	11.6	322	128,000	51	NA	NA	Yes	1	39	Alive
4	NRTI	10.9	524	204,000	<50	NA	NA	Yes	2	38	Alive
5	Protease-inhibitor	7.1	213	176,000	542	NA	NA	Yes	1	41	Alive
6	Observational	1.9	193	124,000	917	NA	NA	No	1	28	Alive
7	NRTI	17.0	331	171,000	257	<50, <50	<50, <50	No	94¶	32	Alive
8	NRTI	26.9	448	28,500	<50	<50, <50	<50, <50	Yes	91‖	40	Alive

* HAART denotes highly active antiretroviral therapy, HIV-1 human immunodeficiency virus type 1, NRTI nucleoside reverse-transcriptase inhibitor, and PCR polymerase chain reaction.
† Adherence issues included an incorrect pill count or self-report of nonadherence at any visit before the first positive DNA PCR result in the infant.
‡ There was unconfirmed transmission from this mother to the infant, who died on day 12, before confirmatory testing.
§ There was no measurement of HIV-1 RNA because the mother died at delivery.
¶ The last negative HIV-1 DNA PCR result was at 28 days.
‖ The last negative HIV-1 DNA PCR result was at 30 days.

2010 WHO PMTCT Guidelines

(WHO leading, countries onboard)

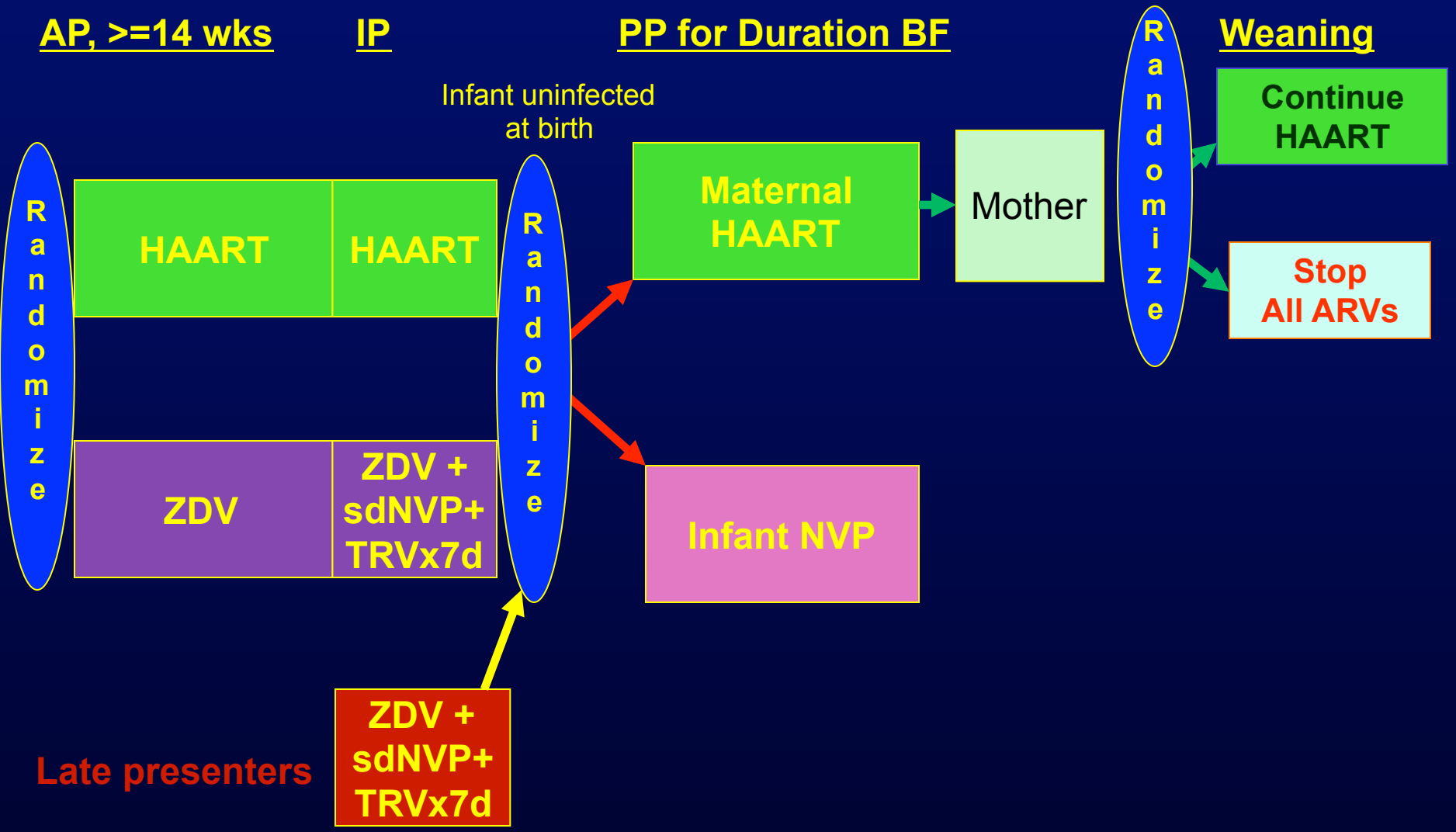
2010 WHO Guidelines: Public Health Approach to PMTCT

- Aspirational: shift to longer / more efficacious PMTCT regimens
  - no sd-NVP option
  - Option B added
- Treatment for those meeting CD4 criteria (< 350) emphasized:
  - CD4 testing / return of results a recognized barrier
- ARV coverage through duration of exposure
  - start at 14 wks gestation, ARVs to mother or infant throughout breastfeeding
- Longer Breastfeeding -- at least 12 mos with ARV coverage

2010 WHO Guidelines	Research / Program Considerations
CD4 < 350 (treatment eligible) Antenatal HAART / postnatal maternal HAART (+ 4-6 wks infant NVP)	-- CD4 threshold likely to increase in keeping with US / Europe
CD4 > 350 <u>Option A</u>: Antenatal AZT / postnatal infant NVP prophylaxis until 1 wk after BF <u>Option B</u>: Antenatal HAART / postnatal maternal HAART / 4-6 wks infant NVP (or sdNVP + AZT, if FF)	-- Option A vs. B efficacy? (PROMISE Study evaluating) -- Risks/benefits of Option B vs. B+, especially EFV teratogenicity -- Countries moving towards B+ ahead of the safety/efficacy data (strong programmatic rationale)
Infant Feeding: Breastfeed with ARV prophylaxis for 12 months	-- Optimal BF duration in setting of HIV exposure unknown

PROMISE Study: Sequential Factorial Trial (BF, non-HAART Std regions)

For Women with CD4 counts > 350



n=4,400 (plus n=2,000 more from FF regions, not shown in diagram)

Maternal ART and Birth Outcomes

- European and African Data: Stillbirths, preterm deliveries, and low birth weight all associated with ART in pregnancy
  - European Data (ECS + Swiss, Townsend, Grosch-Woerner , Boer, Townsend)
  - African Data (Ekouvei, Chen)
- US data: Mixed data, but mostly non-significant effect on birth outcomes
- Problems with most studies:
  - Observational Studies – prone to bias
  - Underpowered for modest increases in risk
  - Some analyses strongly biased by temporal differences in categorizing ART-exposed and –unexposed

Birth Outcomes Surveillance in 6 Botswana District Hospitals

Chen et al, JID 2012

- Prospective review of obstetric and medical records in 6 maternity wards in Botswana
  - Captured ~29% of all deliveries in Botswana during surveillance
- Results (May 2009-April 2011):
  - 33,418 deliveries included
    - Median Age = 25 yrs
    - Nationality: 89% Batswana
    - Marital Status: 82% Single
    - Alcohol: 5%
    - Smoking: 1%
    - Received antenatal care: 95%
  - 32,113 (96%) with HIV test result
  - 9,504 (29.6%) HIV-infected

Birth Outcomes by HIV Status

	HIV− (N=22,609)	HIV+ (N=9,504)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Stillbirth	2.5%	**4.6%**	1.84 (1.63-1.08)	1.52 (1.33-1.74)
Preterm Delivery	17.2%	**23.7%**	1.37 (1.31-1.44)	1.33 (1.25-1.42)
Small for Gestational Age*	11.5%	**18.4%**	1.60 (1.52-1.70)	1.80 (1.68-1.93)
Neonatal Death	1.5%	**2.3%**	1.47 (1.24-1.75)	--

* < 10% using Botswana-specific norms

Risk Factors for Preterm Delivery among HIV+ Women

Risk Factor	% PTD with risk factor	% PTD without risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hypertension in Pregnancy	26.7%	21.3%	1.25 (1.14-1.38)	1.35 (1.19-1.54)
Anemia in Pregnancy	22.7%	4.8%	4.74 (3.88-5.79)	4.12 (2.99-5.68)
CD4 $\leq$ 200 cells/mm^3	20.0%	18.9%	NS	NS
Continued HAART in Pregnancy vs. all others	26.5%	22.7%	1.17 (1.07-1.27)	1.24 (1.10-1.39)
Initiated HAART in Pregnancy vs. ZDV	19.8%	14.2%	1.41 (1.20-1.64)	1.43 (1.15-1.75)

Risk Factors for Small for Gestational Age Infants among HIV+ Women

Risk Factor	% SGA with risk factor	% SGA without risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hypertension in Pregnancy	25.8%	16.9%	1.52 (1.38-1.68)	1.65 (1.45-1.89)
CD4 $\leq$ 200 cells/mm^3	23.4%	15.9%	1.46 (1.25-1.73)	1.71 (1.37-2.13)
Continued HAART in Pregnancy vs. all others	26.1%	15.6%	1.67 (1.53-1.83)	1.83 (1.62-2.08)
Initiated HAART in Pregnancy vs. ZDV	21.5%	14.2%	1.52 (1.32-1.75)	1.45 (1.19-1.79)
Continued HAART vs. Initiated HAART	26.1%	21.6%	1.20 (1.05-1.37)	1.27 (1.03-1.54)

Risk Factors for Stillbirths among HIV+ Women

Risk Factor	% Stillbirths with risk factor	% Stillbirths without risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hypertension in Pregnancy	10.1%	3.3%	3.10 (2.57-3.75)	3.13 (2.53-3.86)
Positive RPR During Pregnancy	7.6%	4.6%	1.67 (0.96-2.90)	1.86 (1.01-3.42)
CD4 $\leq$ 200 cells/mm^3	5.8%	3.6%	1.64 (1.14-2.36)	1.73 (1.17-2.57)
Continued HAART in Pregnancy vs. all others	6.3%	4.1%	1.55 (1.27-1.89)	1.45 (1.15-1.81)
Initiated HAART in Pregnancy vs. ZDV	4.7%	1.7%	2.78 (1.92-4.17)	2.50 (1.64-3.85)

Risk Factor	% Stillbirths with risk factor	% Stillbirths without risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hypertension in Pregnancy	10.1%	3.3%	3.10 (2.57-3.75)	3.13 (2.53-3.86)
Positive RPR During Pregnancy	7.6%	4.6%	1.67 (0.96-2.90)	1.86 (1.01-3.42)
CD4 ≤ 200 cells/mm^3	5.8%	3.6%	1.64 (1.14-2.36)	1.73 (1.17-2.57)
Continued HAART in Pregnancy vs. all others	6.3%	4.1%	1.55 (1.27-1.89)	1.45 (1.15-1.81)
Initiated HAART in Pregnancy vs. ZDV	4.7%	1.7%	2.76 (1.92-4.17)	2.50 (1.64-3.85)

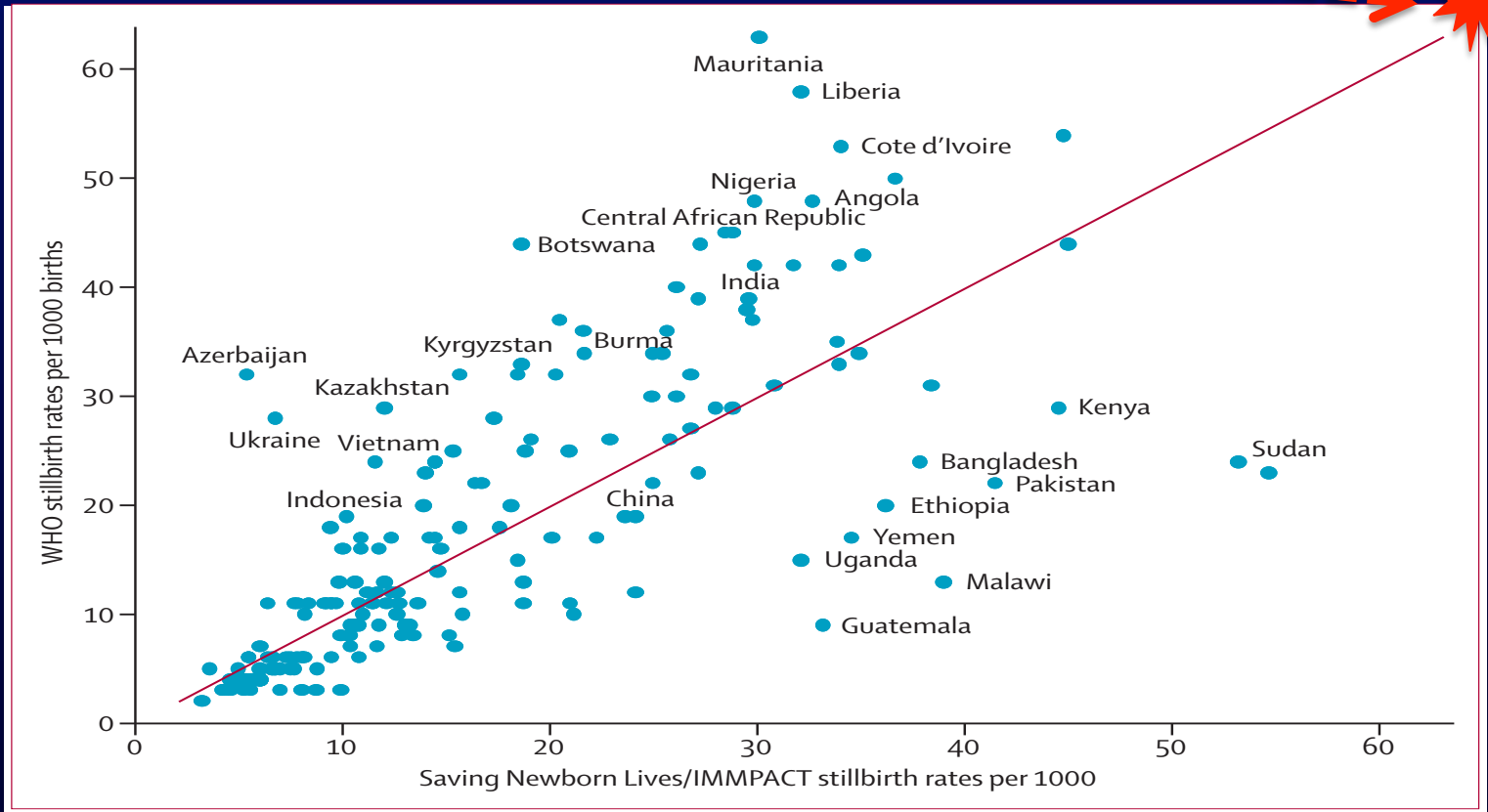


Figure 1: **Data from WHO[1] and Saving Newborn Lives/IMMPACT[2] estimates**
The red line is a 45° line indicating equality between the two sets of estimates. IMMPACT=Initiative for Maternal Mortality Programme Assessment.

Placental Pathology Results in Substudy of 99 Stillbirths

Placental Pathology	HIV+ HAART in pregnancy N=26	HIV+ ZDV in pregnancy N=14	HIV+ No ARVs in pregnancy N=22	HIV- N=37
Chronic hypertensive damage	17 (65%)	6 (43%)	4 (18%)	20 (54%)
Acute hypertensive damage**	1 (4%)	1 (7%)	6 (27%)	3 (8%)
Infection	4 (15%)	3 (21%)	6 (27%)	8 (22%)
Other§	2 (8%)	2 (14%)	0 (0%)	3 (8%)
Unknown	2 (8%)	2 (14%)	6 (27%)	3 (8%)

** 4 women with both acute and chronic hypertensive damage to the placenta were categorized as chronic.
§ Other = maternal floor infarct (2), hydrops fetalis (2), villous maturational arrest (1), massive chronic intervillositis / villitis of unknown/unclear etiology (1), massive perivillous fibrin (1).

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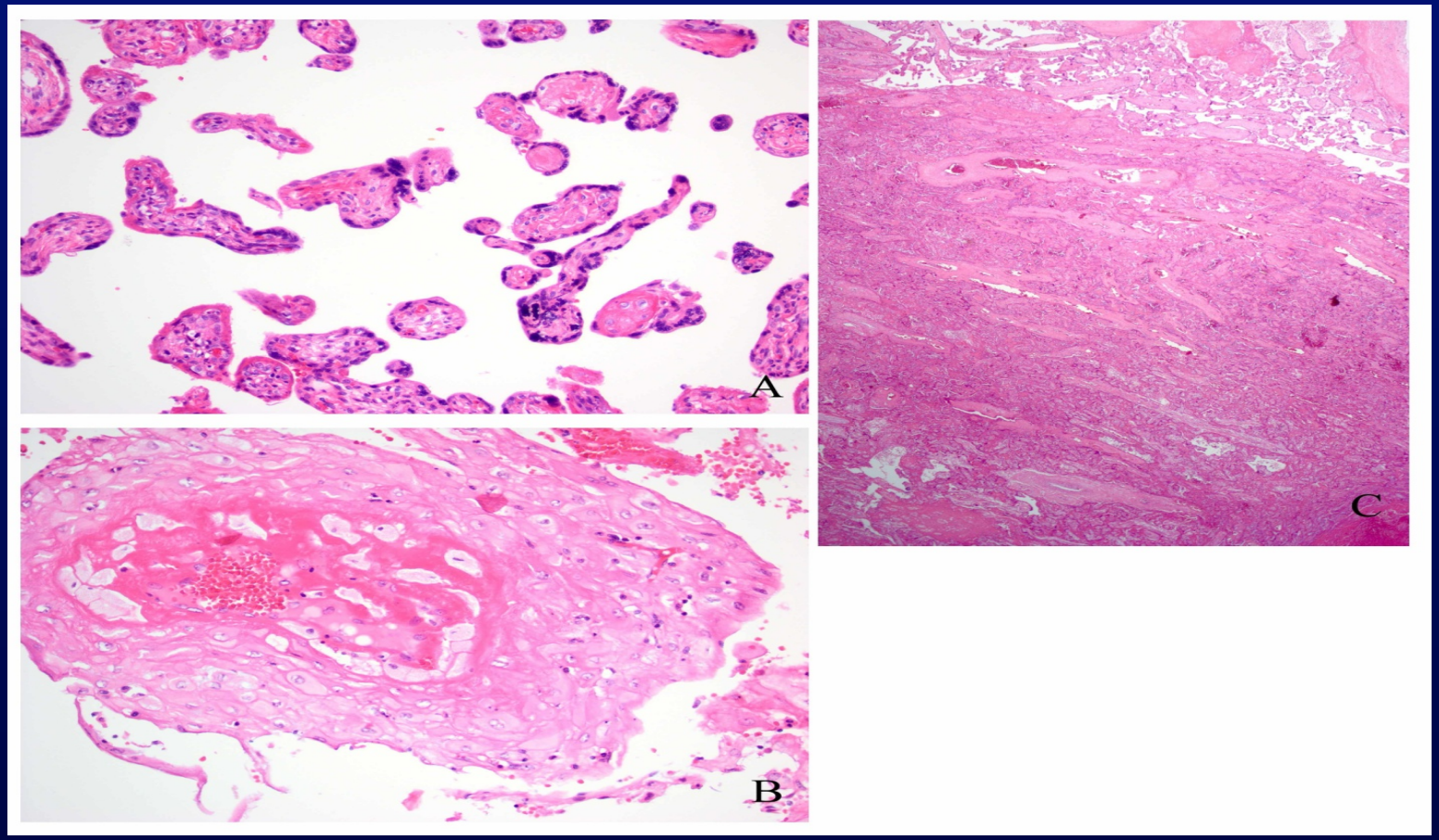
Chronic Placental Hypertensive Damage



H&E stains of placentas with typical characteristics of hypertension: A. Distal villous hyperplasia – small round and elongate villi with large syncytial trophoblastic knots and abundant intervillous space. B. Severe decidual vasculopathy with atherosis. C.Chronic abruption.

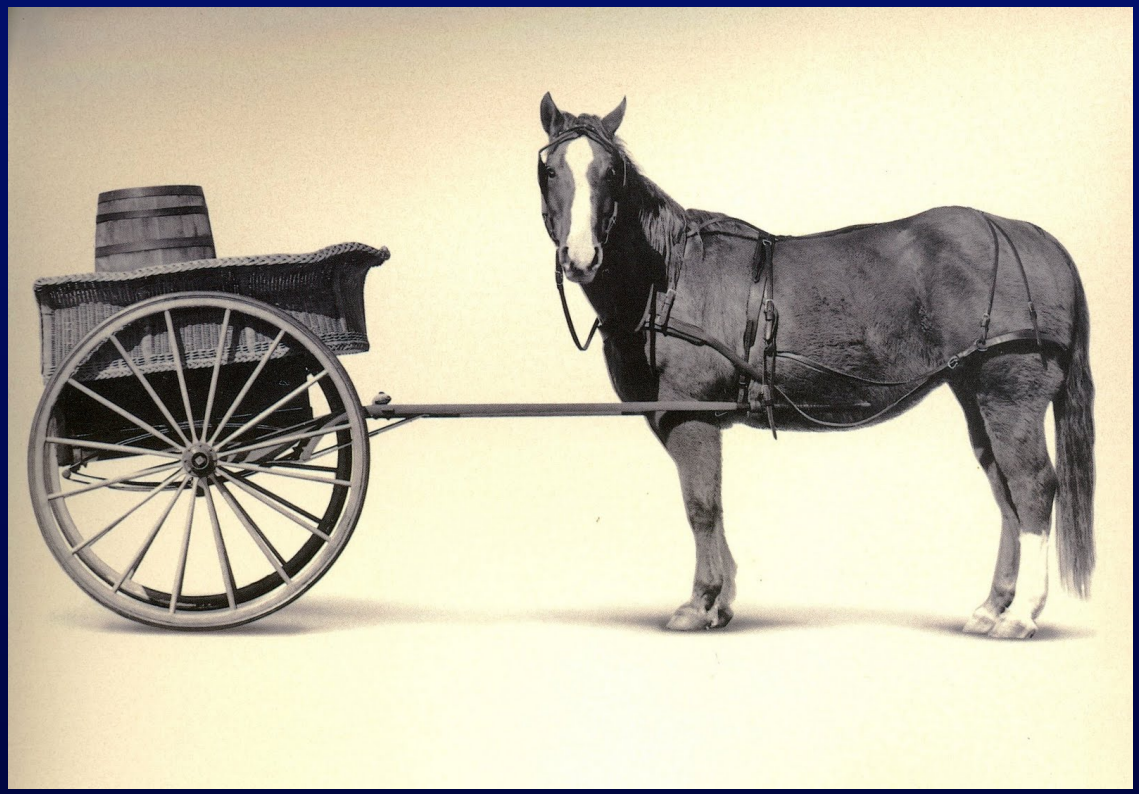
Mma Bana Study: Stillbirths, Prematurity, Low Birth Weight, and Congenital Abnormalities

	Arm A (TZV)	Arm B (KAL/CBV)	Obs Arm (NVP/CBV)
Stillbirths (% of deliveries)	8 (3%)	5 (2%)	11 (7%) (p=0.07 for randomized vs. observational arms)
Live births (including twins)	283	270	156
Preterm Delivery (< 37 weeks*)	42 (15%)	61 (23%) (p=0.04 for Arm A vs. Arm B)	16 (10%)
Low Birth Weight** (< 2.5 kg)	37 (13%)	45 (17%)	23 (15%)
Congenital Abnormality	5 (2%)	5 (2%)	5 (3%)

* Gestational age determined by last menstrual period and/or ultrasound

** Significantly higher rate of LBW than previous non-HAART intervention trial, consistent with another study from West Africa

Program Advances 2010-2013



(countries leading)

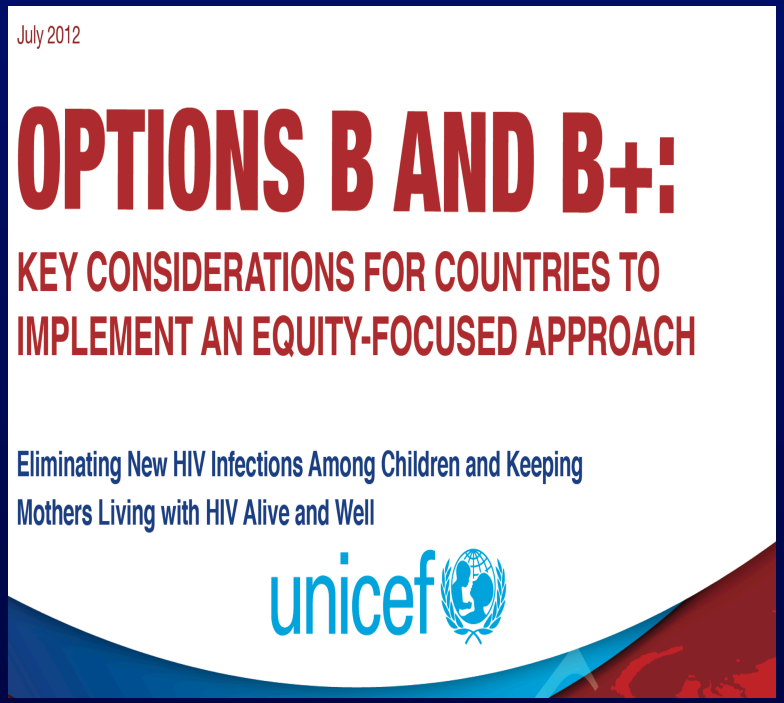
Growing Recognition that Achieving < 2% MTCT Will Require:

1) Political will
2) Facility-based antenatal care
3) Presentation before the 3rd trimester
4) Opt-out, point-of-care HIV testing in pregnancy
5) Linkage to treatment programs
6) …and possibly Option B+

Countries Are Choosing Option B/B+ Rather than Option A

Rationale:

-- Program simplification / coordination with ART programs
--ART now more affordable
-- *Perception* of increased efficacy compared with Option A
-- Avoidance resistance concerns



Pros/Cons of B+

- Advantages of B+ include:
  - No CD4 bottleneck (start everyone), limited or no lab testing
  - Program simplicity (one treatment / PMTCT regimen)
  - Decentralization of ART
  - Future pregnancy protected if late ANC attendance
  - Avoid multiple Option B stops and starts in high fertility regions
  - No limits on breastfeeding
  - Maternal mortality reduction?
  - Treatment as prevention?
- Risks and Unknowns:
  - Only feasible with Atripla – teratogenicity in *future* pregnancy?
  - Pregnancy outcomes with HAART for all HIV+ women?
    - Same as Option B, but earlier exposure in pregnancy
  - Cost / treatment fatigue when starting all HIV+ women
  - Program retention

WHO Guidelines 2013

- Option B+ endorsed by WHO in 2012, after successful rollout in Malawi
  - Support for use of Atripla to use same regimen for PMTCT / treatment
- 2013 Guidelines: will represent an attempt to catch up to where countries are heading….

Scientific Questions about B+

- EFV teratogenicity?
  - Animal data: *In utero* exposure in primates at doses resulting in levels similar to human exposure, 3/20 infant monkeys had severe CNS defects (e.g., anencephaly, cleft palate, anophthalmia).

- **Antiretroviral Pregnancy Registry:**

  Retrospective: 6 human cases of CNS defects (3 neural tube defects such as meningomyelocele)

  Prospective: 2 reports of neural tube / severe facial defects

- **Other data:**

  -- 2011 meta-analysis of 1437 women in 19 studies with first trimester EFV exposure: *NO increased risk of birth defects, 1 neural tube defect (incidence: 0.07%) (AIDS, 2011)*

  -- 4 CNS abnormalities reported from ANRS cohort (CROI 2013)

1st trimester EFV exposure (Fundaro et al. AIDS 2002;16:299-300)

FDA Class D

Scientific Questions about B+

- Will there be less long-term viral resistance compared with Option B (especially in regions with high fertility)?

Scientific Questions about B+

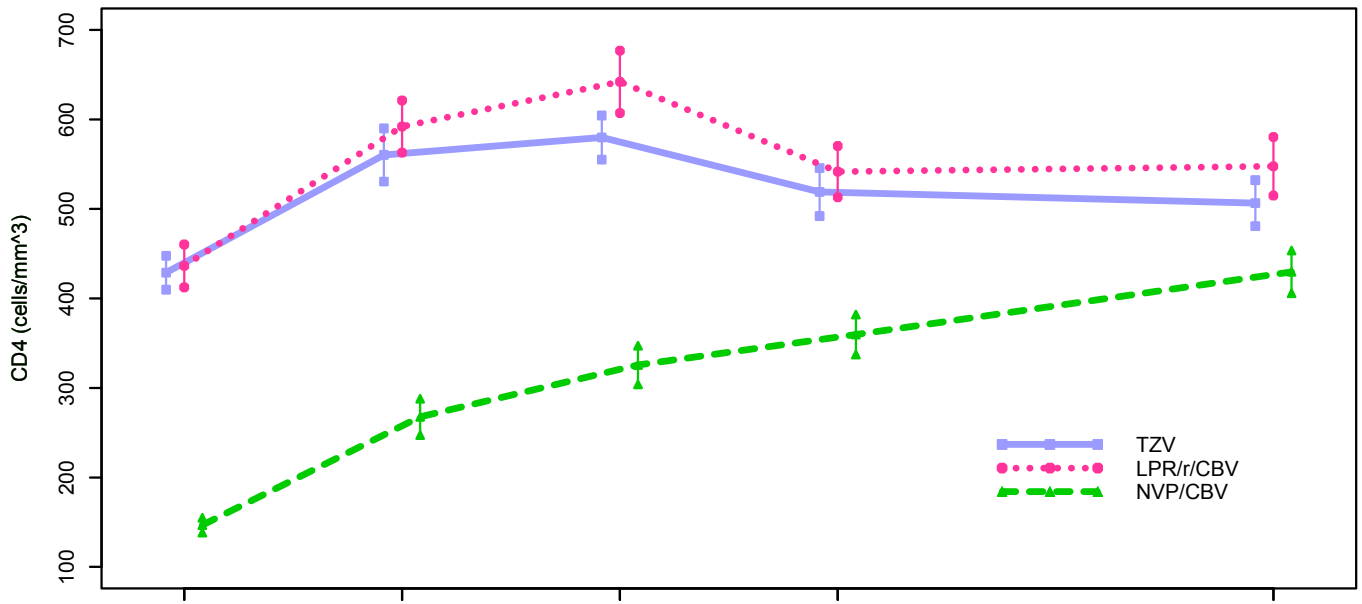
- Mortality advantage compared with B?
  - No Stop/Start (less time with viremia)
  - No reliance on CD4 safety net
- Mma Bana 24 month data (AIDS, 2013)
  - Option B Study (with continuous ART for those < CD4 200/250)

2-year Maternal Results Mma Bana

HAART Status, CD4+ Change, and Maternal Mortality	Total (N=730)	TZV (N=285)	KAL-CBV (N-275)	NVP-CBV (N=170)
Stopped HAART ≤ 6 months	**75%**	95%	97%	4%
Continued HAART past 6 months for treatment	**25%**	5%	3%	96%
Re-started HAART for treatment	**9%**	11%	12%	--
Mean baseline CD4+ cell count (cells/mm^3)	**366**	429	436	146
Mean change in CD4+ at 24 months (cells/mm^3)	**+134**	+68	+98	+283
Maternal Deaths through 24 Months	**14 (1.9%)**	6 (2.1%)	3 (1.1%)	5 (2.9%)

CD4+ Strata	TZV	KAL-CBV	NVP-CBV
0-199	--	--	5 (2.9%)
200-350	2 (0.7%)	2 (0.7%)	--
351-500	2 (0.7%)	0 (0)	--
> 500	2 (0.7%)	1 (0.4%)	--

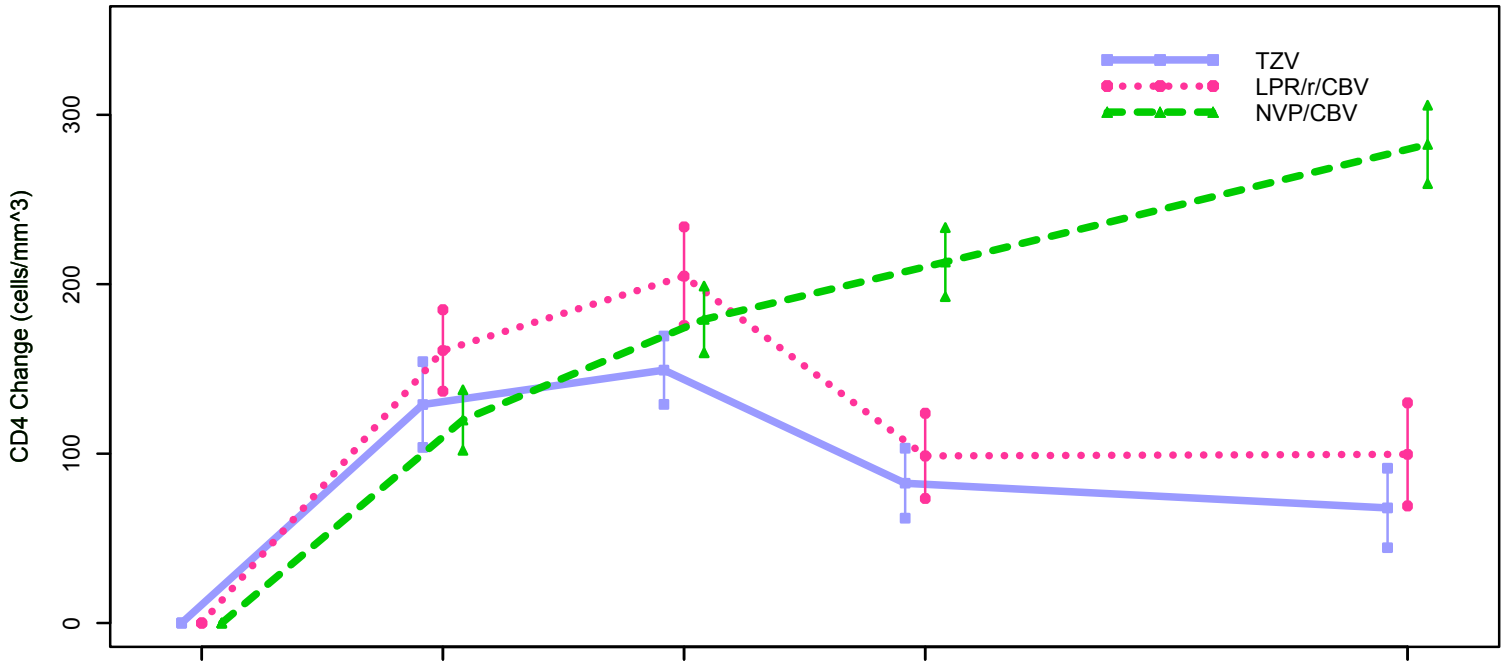
Mean CD4+ Cell Count, by Visit



No. of subjects					
TZV	285	275	261	243	214
LPR/r/CBV	275	263	253	240	202
NVP/CBV	170	160	161	154	145

-- Mean CD4+ cell count increased in all treatment arms (15% of randomized women re-started HAART)

Change in CD4+ Cell Count, by Visit



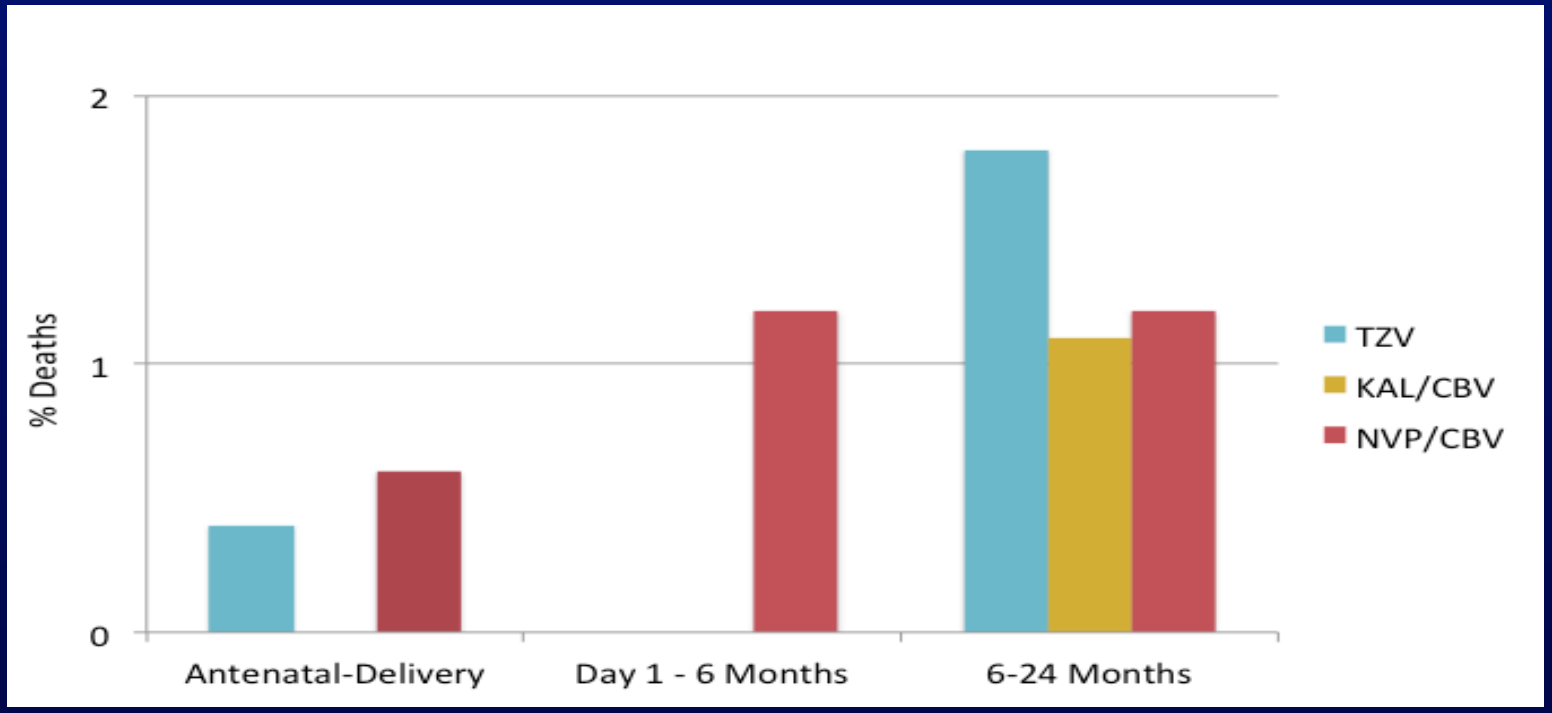
No. of subjects					
TZV	285	275	261	243	214
LPR/r/CBV	275	263	253	240	202
NVP/CBV	170	160	161	154	145

Median Change: TZV +46, LPV/r +86, NVP +275

-- For women with baseline CD4 $\geq$ 250 cells/mm^3, significantly higher CD4 increase with KAL-CBV vs. TZV (86 vs. 46 cells/mm^3, p=0.04)

2-year Maternal Mortality in Mma Bana

Maternal Mortality, by Study Arm and Time Period



8 of 9 deaths among randomized women were from 6-24 months (5 had not re-started HAART)

- **p = 0.18 for deaths < 6 mos vs > 6 mos among randomized women**

Mortality Summary in Mma Bana

-- Mean CD4 counts relatively preserved at 24 months (85% remained off ART)

-- However, 8 of 9 deaths among randomized women were after PMTCT intervention had stopped; 5 of 8 had not re-started ART (4 of 5 with last CD4 > 350, would not be eligible by current guidelines)

Scientific Questions about B+

- Treatment as Prevention?
  - Proven benefits for serodiscordant partners (HPTN 052)

- Cost effectiveness?
  - At least 2 models suggest cost-effectiveness of B+ in African settings, with incremental cost effectiveness ratios of $455 and $1370 per year of life saved (Fasawe *PLoS One* 2013, Ciaranello *CID* 2012)

Conclusions

- Beginning in 2010, WHO guidelines began promoting interventions capable of meaningful MTCT reductions
- Countries are now taking the same approach, rapidly moving to Option B and B+ programs
- As this occurs, program considerations will drive the PMTCT agenda, and recommendations will be aimed at facilitating B+ options for countries (already endorsed by WHO in 2012)
- Scientific agenda will inevitably change
  - Need to monitor unstudied approaches
  - New questions may arise from program data
- Scientists – don't fret!
  - We have reached a tipping point, where the risk from some remaining unknowns pales compared with the benefit of meaningful PMTCT rollout. It is the right thing to do!


Thank You!