



Using new ARVs in pregnancy

Dr Wendy Mphatswe

SA HIV Clinician's Society Meeting
15 July 2017



Overview

1. HIV epidemic
2. HIV response (Fast Track)
3. Goal of therapy in pregnant and breastfeeding women
4. ART guidelines
 - SA Clinical ART guideline
 - WHO clinical guidelines
5. Recent advances
 - PrEP
 - Newer ART agents
6. Safety of ART in pregnancy
7. Conclusion

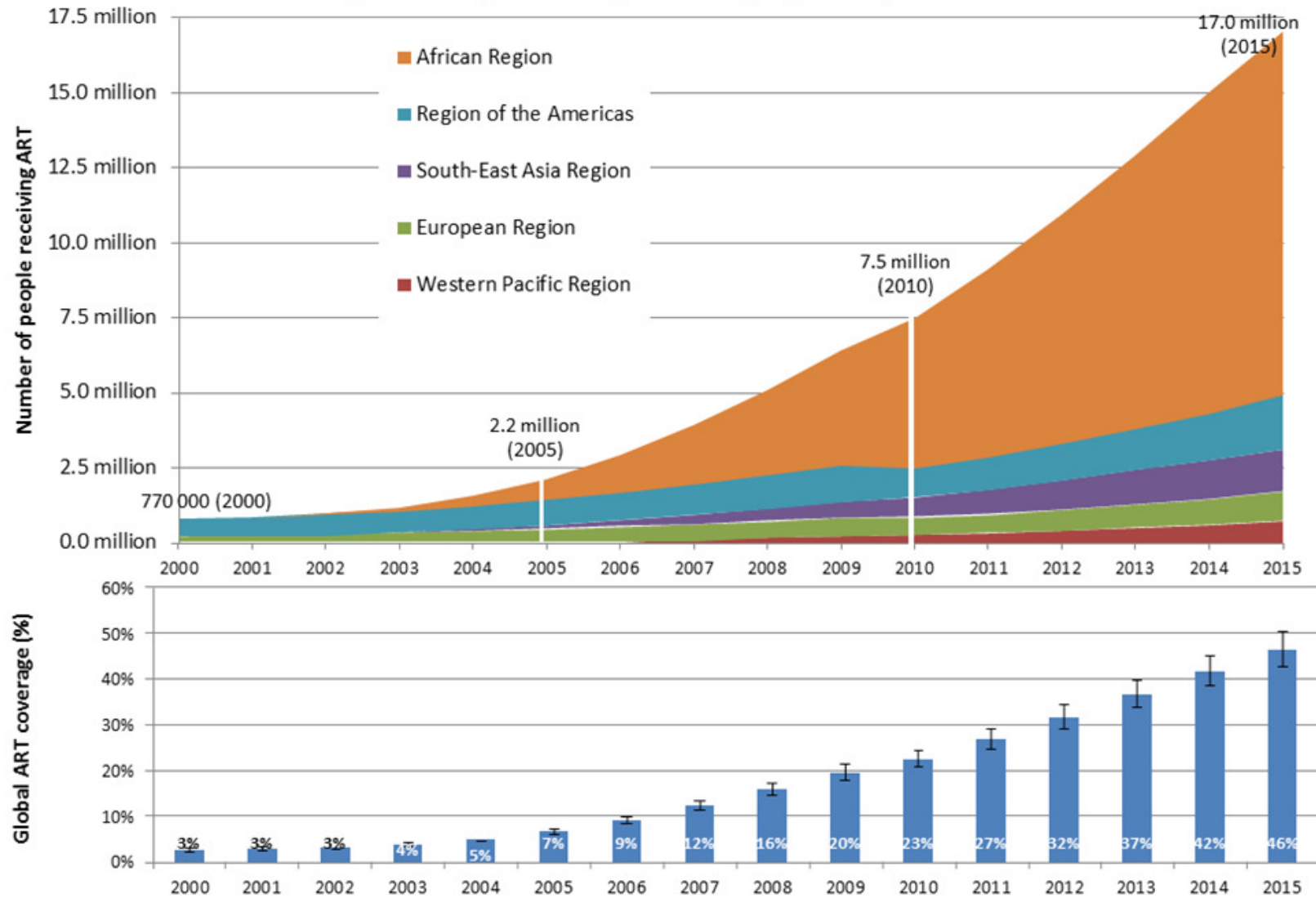
Global summary of the AIDS epidemic | 2015

Number of people living with HIV in 2015	Total	36.7 million	[34.0 million – 39.8 million]
	Adults	34.9 million	[32.4 million – 37.9 million]
	Women (15+)	17.8 million	[16.4 million – 19.4 million]
	Children (<15 years)	1.8 million	[1.5 million – 2.0 million]

People newly infected with HIV in 2015	Total	2.1 million	[1.8 million – 2.4 million]
	Adults	1.9 million	[1.7 million – 2.2 million]
	Children (<15 years)	150 000	[110 000 – 190 000]

AIDS deaths in 2015	Total	1.1 million	[940 000 – 1.3 million]
	Adults	1.0 million	[840 000 – 1.2 million]
	Children (<15 years)	110 000	[84 000 – 130 000]

Estimated numbers of people receiving antiretroviral therapy globally and by WHO Region and percentage coverage globally, 2000-2015



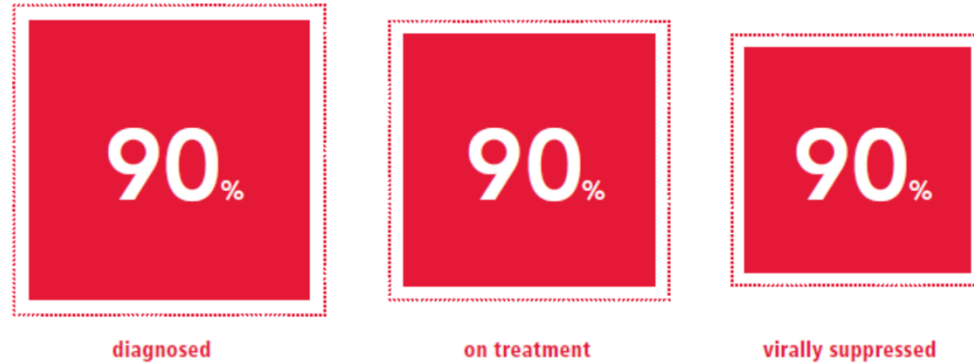
Overall context of the epidemic in SA

- South Africa currently accounts for 17% of the global burden of HIV infection.
- 66% of all new HIV infection are in sub-Saharan Africa
- 6.4 million people living with HIV and AIDS in South Africa (12% of the population)
- > 3 million are on treatment
- South Africa also has the highest burden HIV positive pregnant women in the world.
1,200,000 babies born annually → the HIV prevalence among pregnant women is 29.3% →, almost **360,000 HIV exposed** babies born every year.
- 2.4 million children orphaned due to AIDS

HIV RESPONSE

90 90 90 strategic targets

THE TREATMENT TARGET



- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

The Fast-Track

NO SCALE-UP—maintain 2013 coverage levels

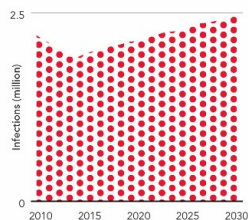


2015

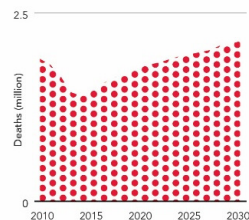


RAPID SCALE-UP—achieve ambitious targets

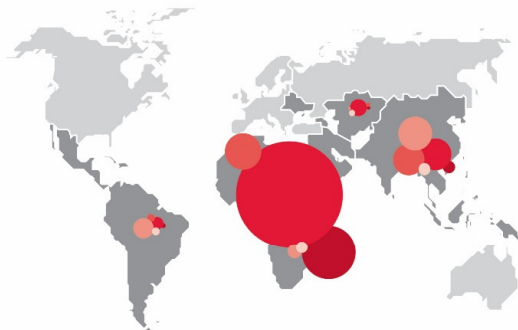
New HIV infections in low- and middle-income countries (millions)



AIDS-related deaths in low- and middle-income countries (millions)



New HIV infections in different population groups, low- and middle-income countries, 2030



- Children
- Heterosexual (including young women, excluding sex work)
- Female sex workers and their clients
- Men who have sex with men
- People who inject drugs

2030

Without scale-up, the AIDS epidemic will continue to outrun the response, increasing the long-term need for HIV treatment and increasing future costs.

MAJOR BENEFITS:

21
MILLION

AIDS-related deaths averted by 2030

28
MILLION

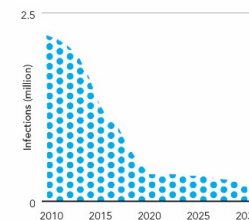
HIV infections averted by 2030

5.9
MILLION

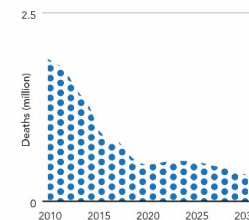
Infections among children averted by 2030

15- FOLD
return on HIV investments

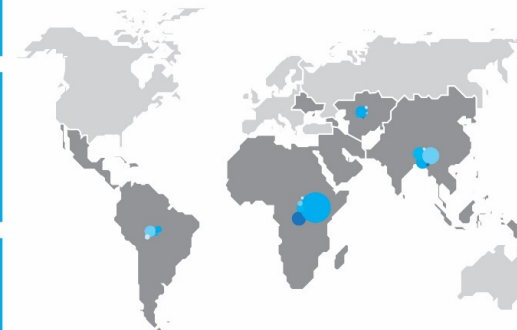
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2030

Rapid scale-up of essential HIV prevention and treatment approaches will enable the response to outpace the epidemic.

Impact of the UNAIDS 90 90 90 strategy

- Modelling suggests that achieving 90 90 90 targets by 2020 will result in the end of AIDS by 2030.
- HIV treatment and viral suppression are critical to the control of the epidemic but this is not on its own.
- Preventative measures need alongside HIV treatment scale up need to be improved simultaneously.

Prevention measures:

- ✓ eMTCT
- ✓ Condom usage
- ✓ Pre-exposure prophylaxis
- ✓ Medical Male Circumcision
- ✓ Focus on key vulnerable populations (Drug users/ MSM etc)

GOALS OF THERAPY IN PREGNANT AND BREASTFEEDING WOMEN

GOALS OF THERAPY IN PREGNANT AND BREASTFEEDING WOMEN

Goal of therapy in pregnant women:

Own health

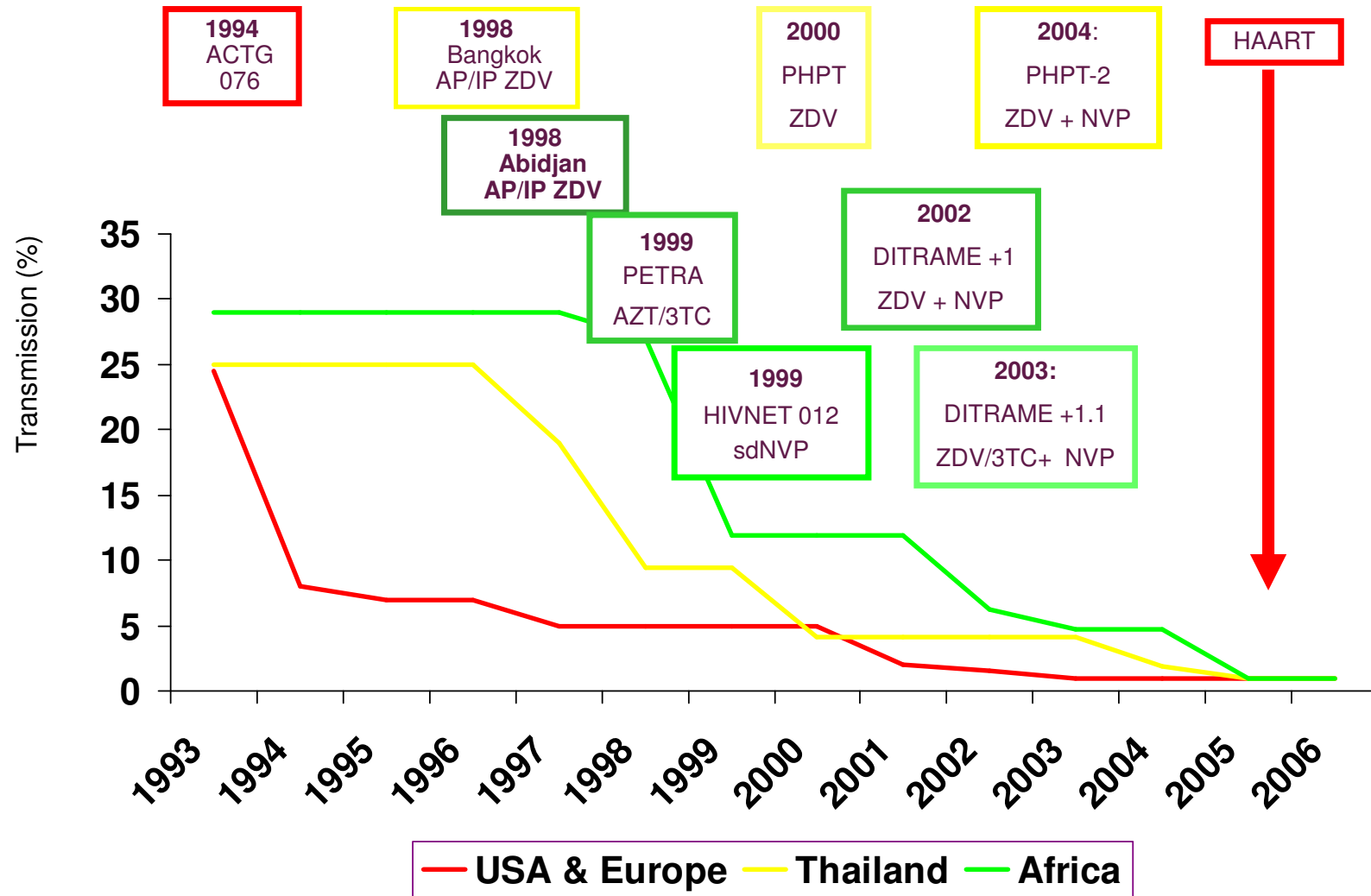
- ✓ Reduce VL to an undetectable level, maintain VL suppression → improve/preserve good immune status → long term survival.

Virtual elimination of mother to child transmission of HIV

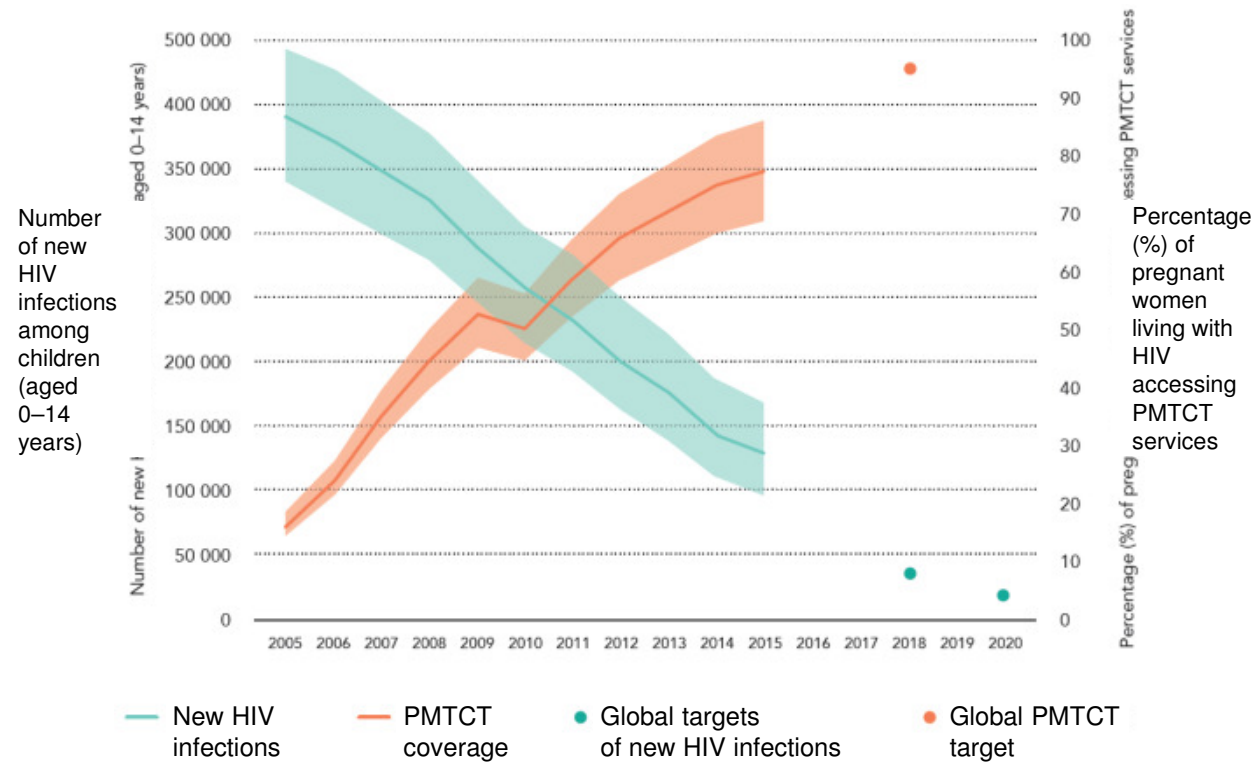
- ✓ Intense monitoring of viral suppression during pregnancy and breastfeeding
- ✓ Rapid response in cases of patient with unsuppressed VL
- ✓ Intensify post-exposure prophylaxis in HIV exposed babies
- ✓ Early HIV diagnosis (repeat testing)

IMPACT OF ART ON MOTHER TO CHILD TRANSMISSION

Trends in reduction of MTCT: study results over time



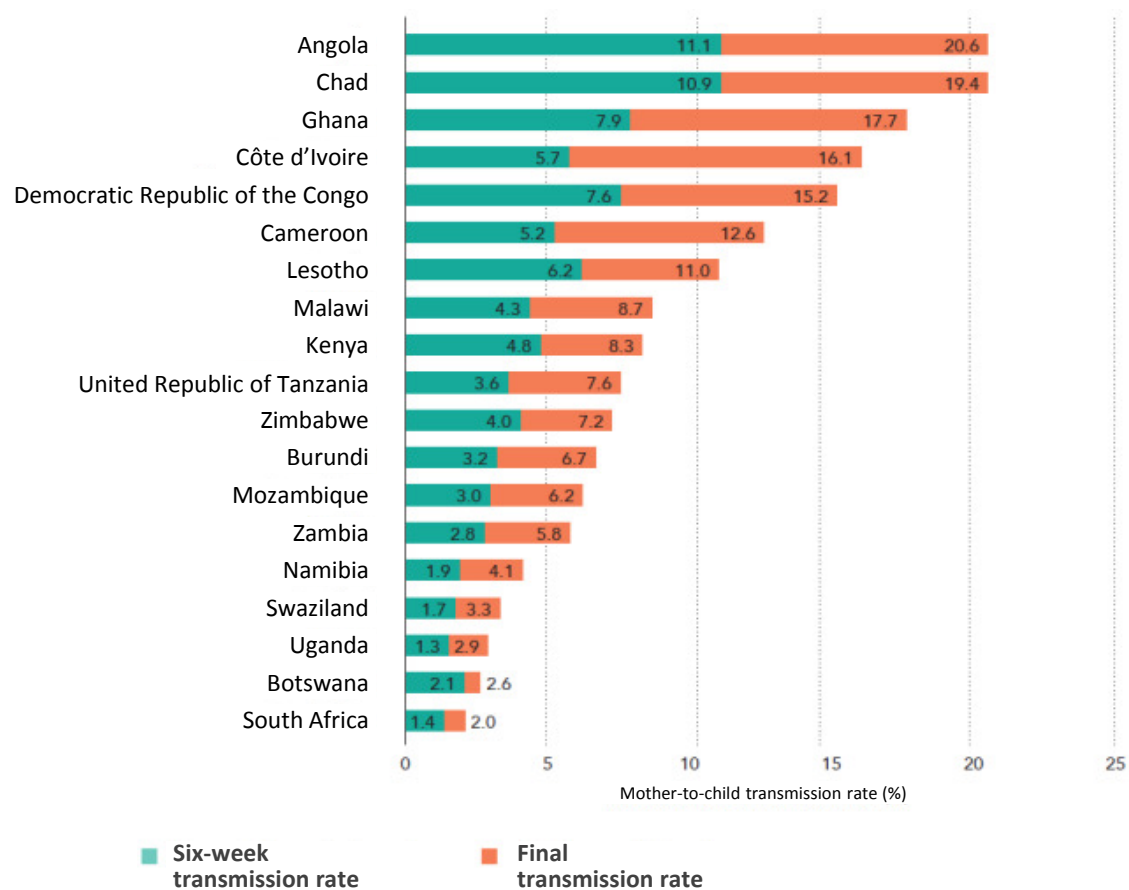
New HIV infections among children (aged 0–14 years) and percentage of pregnant women living with HIV receiving antiretroviral medicines (either prophylaxis or lifelong therapy) to prevent mother-to-child transmission, global, 2005–2015



Source: UNAIDS 2016 estimates.

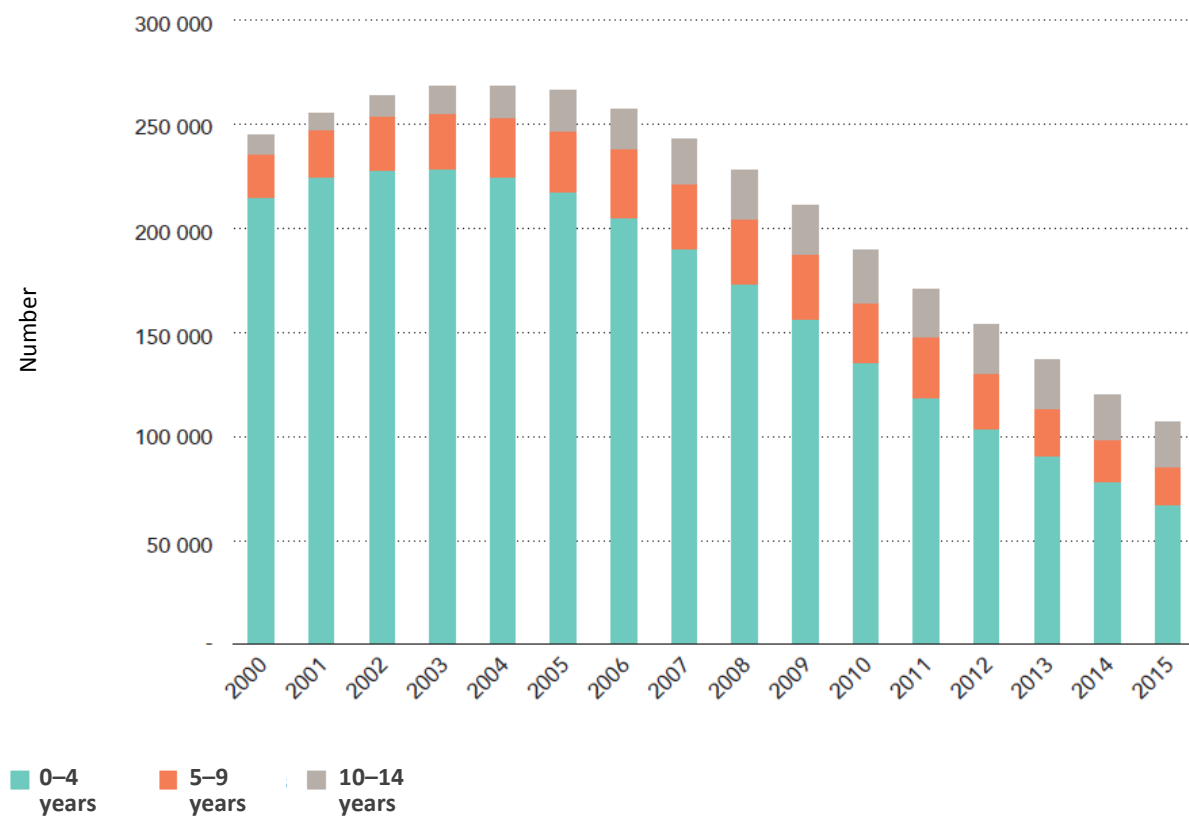
Note: In 2010, single-dose nevirapine was no longer included in ARV coverage as an effective regimen for the prevention of mother-to-child transmission.

Six-week and final mother-to-child transmission rates, by country, 2015



Source: UNAIDS 2016 estimates.

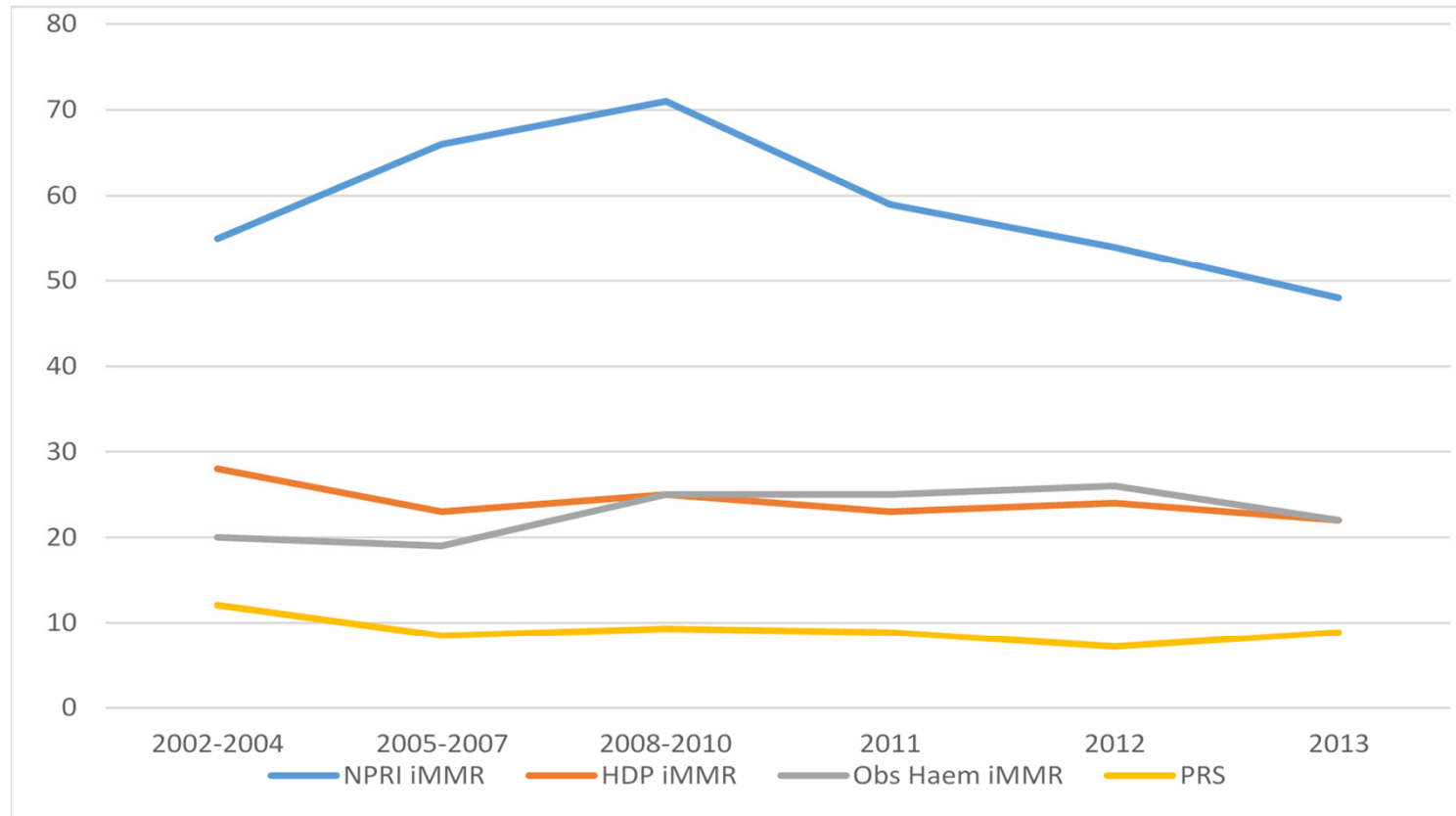
AIDS-related deaths among children by age group, global, 2000–2015



Source: UNAIDS 2016 estimates.

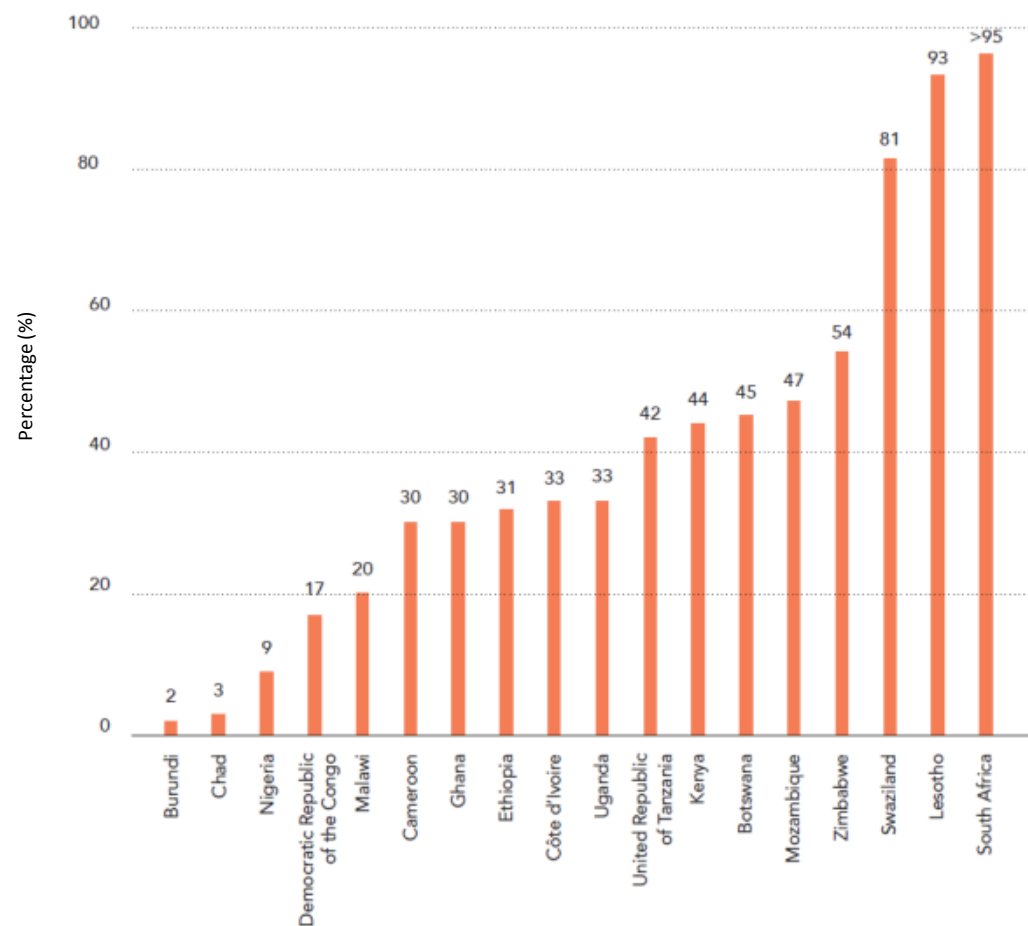
IMPACT OF ART ON MATERNAL MOTARLITY

Figure 1: Impact of HAART on institutional maternal mortality (iMMR): (Adapted from Saving Mothers Report, 2011-2013)



NPRI = non-pregnancy related infections / HDP=hypertensive disorders of pregnancy / Obs haem = obstetric haemorrhage / PRS = pregnancy related sepsis

Percentage of infants born to women living with HIV receiving a virological test within the first two months of life, by country, 2015



Source: 2016 Global AIDS Response Progress Reporting.

SA guidelines 2015



SA guidelines

- From January 2015, all HIV-infected pregnant and breastfeeding women initiated on an EFV-based FDC
- TDF+3TC (FTC)+EFV
- Regardless of CD4 count, WHO stage or infant feeding practice
- FDC continued for life once started

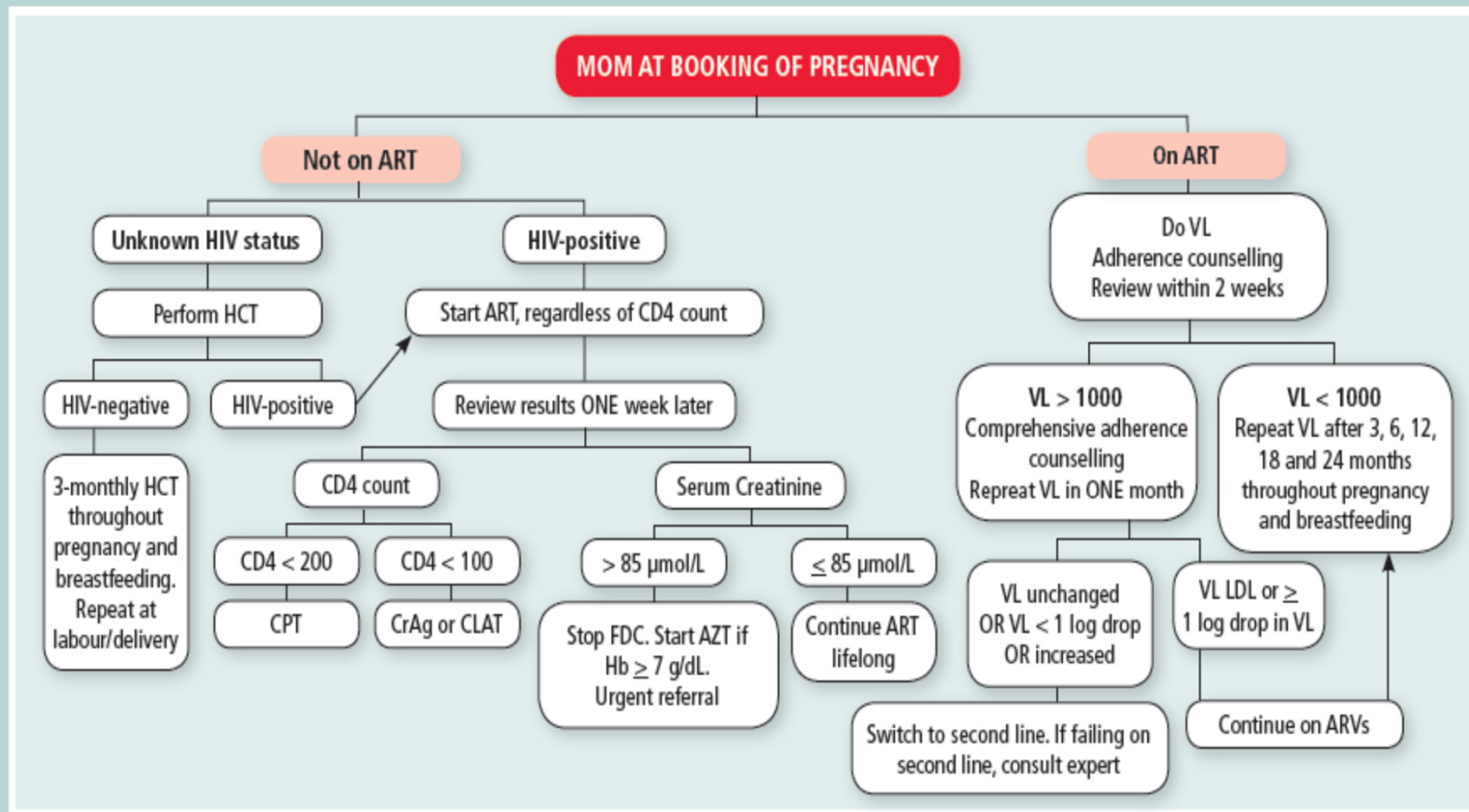
WHO B+ PROGRAM



UNIVERSAL TEST AND TREAT SINCE 2016

SA Guidelines

PMTCT: GUIDELINES FOR PREGNANT WOMEN 2015



ROUTINE MONITORING OF MOTHER	
Test	Purpose and response
FIRST ANC VISIT: PATIENTS WHOSE HIV STATUS IS UNKNOWN/UNCONFIRMED	
HIV Rapid Test and CD4, if HIV-positive	To establish/confirm HIV status CD4 < 200: initiate co-trimoxazole prophylaxis (CPT) CD4 < 100: do CrAg or CLAT CD4 ≥ 250: do NOT use NVP
WHO Clinical Staging, if HIV-positive	To assess risk
Hb or FBC	To detect anaemia and/or neutropaenia
Creatinine*	To assess renal function (and eligibility for TDF)
ALT, if requiring NVP	To exclude liver dysfunction
FIRST ANC VISIT: ALL PATIENTS (ALREADY ON ART AND NEWLY-DIAGNOSED)	
Screen for chronic diseases	To identify high-risk pregnancy
Nutritional assessment	To detect deficiency and provide necessary nutritional support. All pregnant women should get calcium, folate and iron supplementation
Family planning	Provide counselling on safer sex, post-natal contraception, partner testing and cervical cancer screen
TB screening	To identify TB suspects and assess IPT/INH eligibility. If TB is suspected in patients not yet on ART, do not start ART and refer for urgent diagnosis/exclusion of TB: TB diagnosed: start ART 2 – 8 weeks after starting TB treatment TB excluded: start ART
STI and syphilis screening (RPR)	To identify and treat STIs
CrAg (cryptococcal antigen), if CD4 < 100	To treat/provide prophylaxis for cryptococcal meningitis
Hb or FBC	To detect anaemia and/or neutropaenia
PATIENTS ON ART	
CD4 count	At initiation, at 12 months, then yearly, if clinically indicated
Viral Load Be sure to check results and respond quickly!	To detect treatment failure Repeat VL on confirmation of pregnancy if on ART > 3 months, then after 3, 6, 12, 18 and 24 months throughout pregnancy and breastfeeding
ALT, if on NVP, and symptomatic (rash, hepatitis)	To identify NVP toxicity
FBC, if on AZT	Month 3, 6, then yearly. To identify AZT toxicity
Creatinine*, if on TDF	Month 3, 6, 12, then yearly. To identify TDF toxicity

Give adherence counselling at every clinic visit

*Please note that calculated eGFR is not accurate during pregnancy. Serum creatinine and not the eGFR should be used

Based on the National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. National Department of Health, South Africa. April 2015.

SA guidelines

Second-line regimen

Failing on a TDF-based 1st line regimen

- AZT + 3TC + **LPV/r**
- AZT + TDF + 3TC + LPV/r (4 drugs if HBV co-infected)

Failing on a d4T or AZT-based 1st line regimen

- TDF + 3TC (or FTC) + **LPV/r**
- Dyslipidaemia or diarrhoea associated with LPV/r switch LPV/r to **ATV/r**

SA guidelines

Threshold for treatment failure:

- VL>1000, adherence counselling, repeat VL in 1 month
- 2nd VL undetectable or reduction in VL ≥ 1 log (10-fold), continue existing regimen
- VL unchanged or increased, switch to 2nd line therapy

HIV positive women

Baseline Work-up

- Clinical examination (WHO staging)
- Screen for active psychiatric illness
- Bloods: Creatinine and CD4
- Follow-up in 1 week for these blood results

All women, regardless of HIV status:

- TB and STI screen
- BANC: Hb, RPR/rapid TPHA, Rh, Urine dipstix, micronutrients
- Register on Momconnect

HIV positive women

ART Initiation

- Initiate FDC (TDF/FTC/EFV) SAME DAY unless:
 1. Concern about abnormal renal function
 2. ACTIVE psychiatric illness
 3. Newly diagnosed TB or high suspicion of active TB
- All women with contraindication to FDC initiation must receive **AZT 300mg bd** at their first visit
- No woman leaves her first ANC visit without any ARV cover for PMTCT
- Arrange follow-up visit in ONE WEEK (blood results)

Contraindications to FDC (1)

Suspected/Known Renal Dysfunction

- TDF associated with renal toxicity
- DO NOT initiate FDC same day if:
 - Diabetes or hypertension
 - Previous kidney condition requiring hospitalization (excluding UTI)
 - $\geq 2+$ proteinuria on urine dipstix
- Send for creatinine
- **Initiate AZT 300mg bd SAME DAY**
 - As long as Hb ≥ 7 g/dl

Contraindications to FDC (2)

Suspected/Known Renal Dysfunction

- Review in 1 week
 - Creatinine normal: INITIATE FDC
 - Creatinine $\geq 85 \mu\text{mol/L}$ = HIGH RISK PREGNANCY
 - Continue AZT 300mg bd
 - Urgen REFER (or telephonically consult):
 - Initiation of alternative lifelong triple drug regimen, including dose adjustment (usually ABC, 3TC, EFV)
 - Investigation & management of renal disease
- Remember to work up those with $\geq 2+$ proteinuria according to local protocols

Contraindications to FDC (3)

Suspected/Known Renal Dysfunction

- IF woman initiated on FDC at first visit and Creatinine $\geq 85 \mu\text{mol/L}$ at review

CHEMISTRY TESTS		Flags	RefInterval
Creatinine	57 $\mu\text{mol/L}$		49 - 90
MDRD eGFR	> 60		ml/min/1.73m ²

CHEMISTRY TESTS		Flags	RefInterval
Creatinine	133 $\mu\text{mol/L}$	H	64 - 104
MDRD eGFR	50		ml/min/1.73m ²

- STOP FDC
- START AZT 300mg bd (if Hb $\geq 7\text{g/dl}$)



- Urgently refer/discuss telephonically



Contraindications to FDC (4)

Active Psychiatric Illness

- If a woman has ACTIVE/UNTREATED psychiatric disorder:
- DO NOT initiate FDC
- Provide AZT 300mg bd (if Hb $\geq$ 7g/dl)



• HIGH RISK PREGNANCY

• Urgently refer/discuss telephonically



- Initiation of alternative lifelong triple drug regimen (NVP or LPV/r, dependant on CD4 count, plus TDF and 3TC)
 - Optimise management of psychiatric disorder
-
- ACTIVE psychiatric illness DOES NOT INCLUDE
 - Depression
 - Anxiety
 - Known psychiatric patient well controlled/asymptomatic on treatment

TB (1)

Screening

- Screen **EVERY** woman, regardless of HIV status, at **EVERY** visit for TB

TB Screen Negative = IPT

- Negative TB screen (NO cough, fever, night sweats, weight loss/failure to gain weight)
- START IPT and pyridoxine

Duration of IPT	COMMENT
» Tuberculin Sensitivity Test (TST) positive: 36 months	» All should be on lifelong ART
» TST negative: 12 months	» IPT can be started anytime during pregnancy/breastfeeding, but ART should be started first and IPT added after a minimum of 1 month
» TST not available: 12 months	» Woman who fall pregnant on IPT should continue IPT
	» If TST negative, re-assess TST status 1 year after completing IPT

Contraindications to IPT as per adult guidelines

Monitoring During Pregnancy and Breastfeeding

- VIRAL LOAD
- VIRAL LOAD
- VIRAL LOAD

Viral Load Monitoring (1)

Woman Already on ART ≥ 3 months and Conceives

- Viral Load to be repeated **ON THE DAY OF PREGNANCY CONFIRMATION**
 - Regardless of when last done
 - Need to know this woman is virally suppressed
- Review result within **TWO WEEKS**
- If virally suppressed:
 - Continue on current regimen
 - *If on first line single ART agents with no contraindications (check creatinine) – Switch to FDC (TDF/FTC/EFV)*
- Provide adherence counselling including educating about the link between viral load and the risk of MTCT and safety of ART in pregnancy.

Viral Load Monitoring (2)

Woman Newly Initiated on ART

- First viral load will be done **THREE MONTHS** after ART INITIATION
- Review results within **TWO WEEKS**
- We need to know this woman is suppressing on ART

Viral Load Monitoring (3)

Women Who Are Virally Suppressed

- If Viral Load is < 1000 copies /ml
- Repeat Viral Load **SIX MONTHLY**:
- All viral load results should be reviewed within TWO WEEKS
- If **concerns about poor adherence** repeat viral load, regardless of when last done
- Women will return to annual viral load monitoring once she has stopped breastfeeding and is enrolled in standard adult ART care

Viral Load Monitoring (4)

Women with Viral Load >1000 copies/ml

- Intensive adherence counselling
- Repeat **Viral Load** after **ONE MONTH**
PLUS
 - **Hep B sAg**
 - **Hb/Creatinine** (depending on predicted 2nd line regimen)
- **Viral load undetectable OR ≥ 1 log drop**
 - Continue with current ART regimen
 - Monitor adherence closely
 - Repeat viral load in 6 months, or **sooner if concerns about adherence**

Treatment failure:

- **VL>1000**, adherence counselling, repeat VL in 1 month
 - 2nd VL undetectable or reduction in VL ≥ 1 log (10-fold), continue existing regimen
 - VL unchanged or increased, switch to 2nd line therapy

Viral Load unchanged, increased or ≤ 1 log drop

- Switch to 2nd line
 - Regimen as per adult guidelines
- CHECK HEPATITIS B sAg result BEFORE switch
 - Hep B -ve = 3 drug 2nd line regimen
 - Hep B +ve = **4 drug 2nd line regimen INCLUDING TDF**
 - Infant to receive Hep B immunoglobulin and Hep B immunisation at birth

Refer/discuss telephonically if woman already on 2nd/3rd line regimen or you are unsure what to do

Other Monitoring

- Unchanged
- Creatinine: 3, 6, 12 months and annually
- CD4: baseline, 12 months, not again
 - If **CD4 < 200** start **Co-trimoxazole**
 - Or if WHO stage 2, 3 or 4 disease
 - If **CD4 < 100** send **Cryptococcal latex antigen** and follow available protocol and refer if screen positive

Labour and Delivery



Labour and Delivery

- HIV negative
 - Repeat HIV test
 - Regardless of when last done
- HIV status unknown
 - Counsel and provide HIV test
- HIV positive on ART
 - Continue ART with usual timing

Newly Diagnosed HIV Positive:

Unbooked women & previously HIV negative

- In-labour management:
 - Stat sd NVP
 - Stat sdTruvada (FTC/TDF)
 - 3 hourly AZT
- FDC dispensed before discharge to start the following day
 - Counselling and adherence support
 - Take CD4 and Creatinine
 - Review results at 3-6 day post-natal visit

Baby:

- Birth PCR
- 12 weeks NVP
- Repeat PCR at 14 weeks

Safe Delivery Techniques

- Avoid prolonged rupture of membranes
- Use assisted instrumental delivery only if absolutely indicated for obstetric reasons
- Invasive monitoring procedures not used in KZN
- Episiotomy only if essential
- Invasive suctioning of the neonate's nose and airway
 - Meconium stained liquor – suction under direct vision
- **Caesarean section**
 - All HIV-positive women to receive prophylactic antibiotic
 - If HIV-positive and not on ART, sdNVP and Truvada beforehand

Post-partum



Within one hour of delivery

ALL Infants

- Skin-to-skin contact with mother asap
- Initiate exclusive breastfeeding
- Teach mother about kangaroo mother care

As soon as possible after birth...

HIV-exposed infants

- Initiate infant prophylaxis
- Infant birth PCR

Testing

Test	When	Who	Where	What
1	Birth	All exposed	Nursery/ Post natal ward	PCR
2 NON- BF	10/52	All exposed infants getting 6/52 NVP	PHC Clinic	PCR
	OR			
	14/52	All exposed infants getting 12/52 NVP	PHC Clinic	PCR
3	6/52 post B/F	All exposed infants who are B/F	PHC Clinic	PCR
4	18/12	All exposed infants	PHC Clinic	Rapid test

Most Infants

Infant Prophylaxis		
Infant	Regimen	Comment
Mother on lifelong ART	NVP at birth and then daily for 6 weeks	

- These mothers are expected to be virally suppressed
 - infant does not need extended NVP cover for breastfeeding
- 6 monthly maternal viral load monitoring essential
 - URGENT intervention if Viral Load >1000 copies/ml beyond 6 weeks of breastfeeding

Infants who need additional prophylaxis

12 weeks NVP	6 weeks NVP plus AZT
Infants born to mothers who have not been on ART for long enough to be virally suppressed by the time the infant is 6 weeks old: • < 4 weeks on ART • Diagnosed in labour/delivery • Diagnosed during breastfeeding and still breastfeeding	Infants born to mothers who have been on ART for > 3 months and still have a viral load >1000 copies/ml. • These women may have poor adherence • These women may have ART resistance

Mothers Failing 2nd/3rd Line

- If mother has VL > 1000 copies/ml and is on SECOND or THIRD LINE therapy:
 - This baby **should preferably not be BREASTFED**
 - **Prescribe infant formula** (medically indicated)
 - Need to ensure facilities have stock
- If formula not available:
 - Careful counselling of mother
 - Intensive adherence support
 - Exclusive breastfeeding



**These mother-baby pairs should be referred/
telephonically discussed**



Other Infants

- **Orphaned/Abandoned** with unknown maternal status
 - Give NVP immediately
 - Test infant with HIV rapid test
 - If rapid test positive AND do birth PCR: continue NVP for 6 weeks
 - If rapid test negative: stop NVP
- **Non-breastfeeding** mother diagnosed HIV positive > 72 hours after delivery
 - No infant NVP
 - Perform PCR at maternal diagnosis:
 - If positive, initiate ART, CPT and confirm with second PCR
 - If negative: continue with infant testing algorithm up to 18 months

After Delivery, Before Discharge

- Dispense minimum 8 weeks ART to mother
- Ensure mother understands about:
 - ART adherence
 - Infant prophylaxis dosage and adherence
 - Exclusive breastfeeding
 - Where and when to follow-up for herself plus her infant
- Discuss/offer contraception
- Clearly document management plan for mother-baby pair in RTHB

Infant Feeding

- All infants, regardless of maternal HIV status, should be exclusively breastfed
- Unless medically indicated:
 - Mother or infant physically incapable
 - Non-ART medications not suitable for breastfeeding
 - Mother on 2nd or 3rd line therapy and viral load >1000 copies/ml
 - These infants must receive PRESCRIBED FORMULA
- OR mother chooses not to breastfeed
 - Support her choice
 - Educate appropriately about formula feeding
 - Ensure has resources to provide formula for baby

Breastfeeding

- Repeated feeding counselling – reinforce messaging
- **6 months exclusive** breastfeeding
 - No water, pap, other solids
 - Can give medication
- Introduction of complementary foods only from 6 months
- **Continue** breastfeeding:
 - 12 months if mother HIV positive
 - 24 months if mother HIV negative (remember repeat HIV testing!)
 - 24 months if infant confirmed HIV positive

WHO guidelines 2015



WHO guidelines 2015

Increasing evidence to support earlier ART initiation among all adults as described in the previous section, as well as widespread uptake of option B+ and emerging programme data on the success of option B+ in practice, all support a revised recommendation in 2015 that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment regardless of clinical or CD4 stage of disease. As a result, option B is no longer relevant.

WHO guidelines 2016

A blue and white badge with the word "NEW" in white capital letters on a blue background.

Recommendation

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).

Source: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (<http://www.who.int/hiv/pub/guidelines/adolescents/en>).

WHO guidelines 2016

- Recommendation applies to breastfeeding and non-breastfeeding populations
- Health benefits of universal ART for pregnant and breastfeeding women outweigh potential harm
- Health benefits – immunological and clinical

WHO guidelines 2016

Pregnant or breastfeeding women

Preferred 1st line regimen

- TDF + 3TC (or FTC) + EFV

Alternative 1st line regimens

- AZT + 3TC + EFV (or ~~NVP~~)
- TDF + 3TC (or FTC) + ~~NVP~~

ABC or boosted PIs (ATV/r, DRV/r, LPV/r)
in special circumstances

WHO guidelines 2016

Pregnant or breastfeeding women

Preferred 2nd line regimen

- 2 NRTIs + ATV/r or LPV/r

Alternative 2nd line regimen

- 2 NRTIs + DRV/r

(similar to adults and adolescents)

PRE-EXPOSURE PROPHYLAXIS IN PREGNANCY

WHAT IS PrEP?

PrEP is the daily use of oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) to prevent HIV acquisition.

Effective in HIV populations is great risk of HIV acquisition

- ✓ Benefit in clinical practice if adherent
- ✓ Taken for sufficient duration of therapy
- ✓ Should be used in combination with other prevention tools eg. HIV and STI testing, condom and condom compatible lubricant dissemination, STI treatment, and risk reduction counselling.

IT IS AN ADDITIONAL PREVENTION METHOD!!!



health

Department:
Health
REPUBLIC OF SOUTH AFRICA

National Policy on HIV Pre-exposure Prophylaxis (PrEP)
and Test and Treat (T&T)

FINAL DRAFT - 5 MAY 2016

No mention of pregnancy

No explicit description or outline of “AT RISK POPULATIONS FOR HIV”

TECHNICAL BRIEF

PREVENTING HIV DURING PREGNANCY AND BREASTFEEDING IN THE CONTEXT OF PREP

JULY 2017



WHO RECOMMENDATIONS ON PREP

2015

2015 WHO RECOMMENDATION ON PREP

Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

High quality evidence, strong recommendation

2016

The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection consider the use of PrEP during pregnancy and breastfeeding and state that, in PrEP trials, exposure to TDF-containing PrEP during the first trimester of pregnancy was not associated with adverse pregnancy or infant outcomes (2). The WHO guidelines development group concluded that in such situations the risk of HIV acquisition and accompanying increased risk of mother-to-child HIV transmission (MTCT) outweigh any potential risks of PrEP, including any risks of fetal and infant exposure to TDF in PrEP.

2017

Existing safety data supports the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection

WHO RECOMMENDATIONS ON PREP

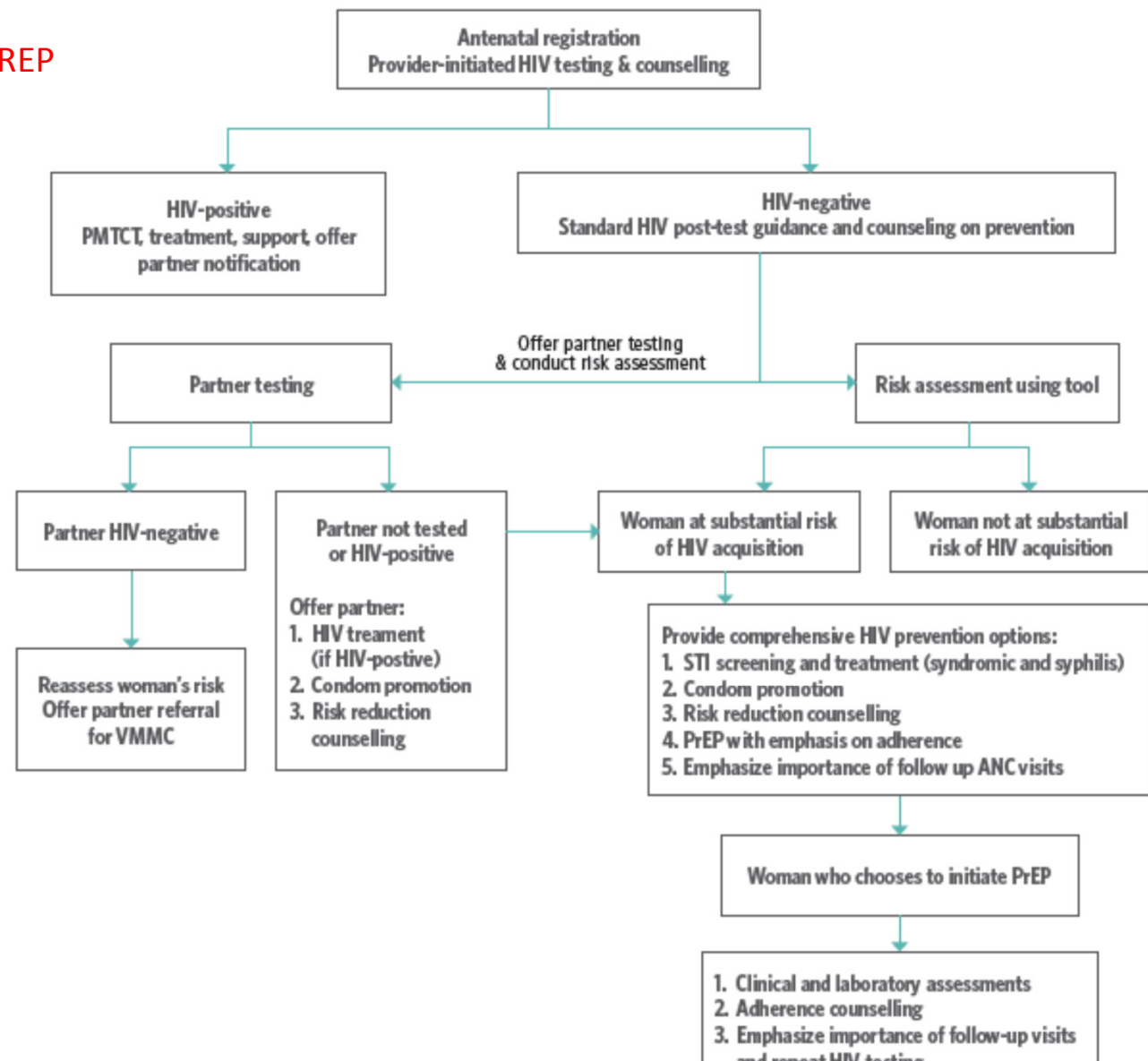
JULY 2017....

Key messages

- **PrEP is safe during pregnancy and breastfeeding.** The ARVs used for PrEP, TDF and TDF/FTC, are frequently used in combination with other ARVs for HIV treatment. The latest WHO systematic review suggests that there does not appear to be a safety-related rationale for disallowing or discontinuing PrEP during pregnancy and breastfeeding for HIV-negative women who are at continuing risk of HIV acquisition.
- **PrEP could be provided as part of a comprehensive package.** PrEP is part of a package of combination HIV prevention and other services that includes HIV testing services, assisted partner notification, provision of male and female condoms and lubricants, contraception choices and screening and treatment of STIs.
- **Adherence matters.** When women understand the benefits of PrEP and want to take it, they are more likely to adhere to it. Some women will find their own ways to maintain adherence to daily PrEP; others will benefit from advice and support. Adolescents may need special support for adherence.
- **Disclosure can have benefits.** Some women may find disclosure of their PrEP use to their partners helpful in supporting their own adherence.
- **Recognize "seasons of risk".** A woman's risk may vary over time as circumstances change. Women should be supported to start and to stop PrEP if their HIV risk changes. Risk for HIV acquisition is not constant.
- **Hormonal contraception.** PrEP can be used with hormonal contraception. Recommended PrEP regimens do not appear to alter the effectiveness of hormonal contraception.
- **PrEP can be cost-effective.** A recent analysis found that providing PrEP to HIV-negative pregnant and breastfeeding women at high HIV risk in sub-Saharan Africa was cost-effective (11).
- **PrEP is not for everyone.** It is a choice, and women should be making an informed decision based on their risk for HIV.
- **Ongoing surveillance is necessary.** Active surveillance of pregnant and breastfeeding women receiving PrEP is needed as countries begin to implement PrEP in this population. National surveillance should identify and record adverse pregnancy and infant outcomes.

Figure 2. A suggested prioritization framework for offering PrEP to pregnant and breastfeeding women (4)

WHO RECOMMENDATIONS ON PREP



Challenges with PrEP in pregnancy and breastfeeding

- Assessment of risk of HIV acquisition
 - Tendency to underestimate or overestimate risk
 - PREVENTION PARADOX (individual risk vs population risk)
 - Absence of objective tools to assess risk
- Safety issues of ART exposure (risk vs benefit) in an HIV uninfected person

BEARING IN MIND...

In SA approximately 4% of pregnant women who initially test HIV negative in early pregnancy are HIV positive later in pregnancy.

New infection → high viral load → high risk for MTCT

NEWER HIV ARVS

Newer antiretrovirals

- ✓ Dolutegravir (DTG)
- ✓ Tenofovir alafenamide (TAF)
- ✓ Efavirenz 400mg (EFV400)

Newer antiretrovirals

- ✓ Dolutegravir (DTG)
 - Possible use as part of 1st line Rx instead of EFV
 - Late presentation in pregnancy → rapid decline of VL (7 days vs 26 days in cART)
 - Intensify treatment (additional 4th agent)
 - Drug resistance (PI based regimens still preferred in drug-resistance case)
- ✓ Tenofovir alafenamide (TAF)
- ✓ Efavirenz 400mg (EFV400)

No sufficient clinical experience of dolutegravir (DTG), tenofovir alafenamide (TAF) or efavirenz 400mg (EFV400) to recommend their use in pregnancy.

Outcomes from births and assessment of congenital anomalies need to be evaluated from several hundred pregnant women.

Integrase inhibitors in late pregnancy and rapid HIV viral load reduction

Am J Obstet Gynecol. 2016 March ; 214(3): 385.e1–385.e7. doi:10.1016/j.ajog.2015.12.052.

1-log reduction, the median time to one-log RNA reduction was 8 days [Interquartile Range (IQR): 7, 14] in the INSTI group versus 35 days



When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO Think Tank

Marco Vitoria^a, Nathan Ford^a, Polly Clayden^b, Anton L. Pozniak^c, and Andrew M. Hill^d



Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding

Amy L. Slogrove^{a,b}, Polly Clayden^c, and Elaine J. Abrams^{d,e}

ART EXPOSURE IN-UTERO

Issues of concern

- Risk of congenital abnormalities
- Pregnancy outcomes
- Cognitive and neurodevelopmental outcomes
- Altered immune activation

Safety concerns: ART exposure

More fetuses and infants are exposed to multiple drugs ART from conception through to breastfeeding.

Risks of EFV in first trimester:

- Known to be associate with CNS abnormalities in animal studies and a recent observational study.
- Ford *et al.* meta-analysis found no increased risk of overall birth defects in infants born to women on EFV [RR] 0.87; 95% [CI], 0.61–1.24).
- Data still insufficient to rule out low-incidence birth defects.

Risk of preterm labour:

- Watts *et al.*: PI based regimens (USA) associated with increased risk of preterm birth started in 1st trimester. No increased risk with NNRTI-based regimens, triple nucleoside regimens, or ARV exposure starting later in pregnancy.

J Infect Dis 2013; 207:612–621

Safety of EFV in pregnancy

- Previous concerns about risk of teratogenicity with use in the 1st T
- Evidence was based on animal studies and retrospective case reports of neural tube defects in infants exposed to EFV in utero
- ✿ ... data from large observational studies don't show an increased risk of neural tube defects with EFV use in all trimesters of pregnancy

Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

**Nathan Ford^a, Lynne Mofenson^b, Zara Shubber^c, Alexandra Calmy^{d,e},
Isabelle Andrieux-Meyer^e, Marco Vitoria^a, Nathan Shaffer^a and
Françoise Renaud^a**

AIDS 2014, **28** (Suppl 2):S123–S131

Discussion: 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, similar to previous systematic reviews. This review contributed to the evidence base for the revised 2013 WHO guidelines on antiretroviral therapy, which

Safety of TDF in pregnancy

Concerns about...

- Congenital abnormalities
- Growth restriction
- Loss of bone mineral density (maternal and fetal)
- Low birth weight
- Preterm delivery
- Pregnancy losses

In Utero Tenofovir Exposure Is not Associated With Fetal Long Bone Growth

Jennifer Jao,¹ Elaine J. Abrams,^{2,3} Tamsin Phillips,⁴ Greg Petro,^{4,5} Allison Zerbe,² and Landon Myer^{4,6}

¹Department of Medicine and Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, ²ICAP, Mailman School of Public Health, and ³College of Physicians and Surgeons, Columbia University, New York, New York; Divisions of ⁴Epidemiology and Biostatistics, ⁵Obstetrics & Gynaecology, and ⁶Desmond Tutu HIV Centre, University of Cape Town, South Africa

There was no association between duration of in utero TDF exposure per 1-week increment and change in FLZ ($\beta = .00$; $P = .51$) or change in HLZ ($\beta = .00$; $P = .40$).

**Tenofovir exposure *in utero* and linear growth
in HIV-exposed, uninfected infants**

Stanzi M. le Roux^{a,b}, Jennifer Jao^{c,d}, Kirsty Brittain^{a,b},
Tamsin K. Phillips^{a,b}, Seun Olatunbosun^{a,b}, Agnes Ronan^{a,b},
Allison Zerbe^e, Elaine J. Abrams^{e,f} and Landon Myer^{a,b}

These data suggest no association between duration of TDF exposure in utero and early linear growth.

Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy

George K. Siberry,¹ Denise L. Jacobson,² Heidi J. Kalkwarf,³ Julia W. Wu,⁴ Linda A. DiMeglio,⁵ Ram Yagev,⁶ Katherine M. Knapp,⁷ Justin J. Wheeler,⁸ Laurie Butler,⁹ Rohan Hazra,¹ Tracie L. Miller,¹⁰ George R. Seage III,⁴ Russell B. Van Dyke,¹¹ Emily Barr,¹² Mariam Davtyan,¹³ Lynne M. Mofenson,¹ and Kenneth C. Rich¹⁴; for the Pediatric HIV/AIDS Cohort Study

“Maternal tenofovir use is associated with significantly lower neonatal BMC. The duration and clinical significance of this finding should be evaluated in longitudinal studies.”

Safety concerns: ART exposure

DART trial: No evidence that **TDF** had adverse effects on pregnancy outcomes or on congenital, renal, bone, or growth abnormalities up to age 4 years. N= 226, 182 enrolled). PLoS Med 2012; 9:e1001217

- Concern that in utero AZT exposure could be associated with paediatric mitochondrial disorders.

Ultimately any ARV use during pregnancy is **NOT** without risk to the fetus.

Surveillance for birth defects and adverse outcomes is warranted given the large number of women who will fall pregnant on ART with B+.

Adverse pregnancy outcomes



Adverse pregnancy outcomes

- Suggestion that cART is responsible for increased risk of adverse pregnancy outcomes

Conflicting results from different studies:

- Different populations studied
- Available obstetric care
- Adjustment for confounders; selection of exposure categories
- ?Inflammatory effect of HIV infection

Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis

Olalekan A Uthman, Jean B Nachega, Jean Anderson, Steve Kanfers, Edward J Mills, Françoise Renaud, Shaffiq Essajee, Meg C Doherty, Lynne M Mofenson

Lancet HIV 2017; 4: e21–30

Background

- Systematic review of studies from low-, middle- and high-income countries
- Studies done between January 1980 and June 2016
- **1° measure:** to assess association between selected pregnancy outcomes and ART initiation pre-conception vs. after conception

Results

- 11 studies with 19 189 mother–infant pairs
- Women who started ART before conception significantly more likely to:
 - ☐ deliver preterm (RR 1·20, 95% CI 1·01–1·44)
 - ☐ very preterm (1·53, 1·22–1·92)
 - ☐ have LBW infants (1·30, 1·04–1·62)
- ...than were those who began ART after conception

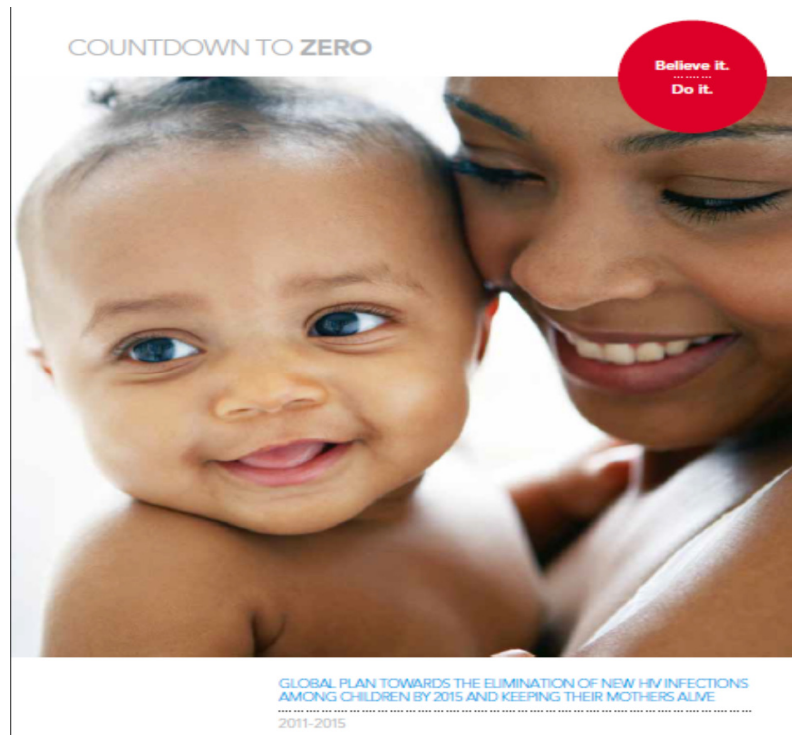
CONCLUSION

Lifelong ART for pregnant and breastfeeding women → Universal ART

Safety data of cART is encouraging and reassuring

PrEP is recommended in pregnant and breastfeeding women who are at high risk for HIV acquisition

Not enough experience with newer ART agents



“No child should be born with HIV;
No child should be an orphan because of HIV;
No child should die due to lack of access to treatment.”

Ebube Sylvia Taylor, 11-years – Nigeria

THANK YOU