British HIV Association BHIVA

marking World AIDS Day

FHIVA federation of hiv associations

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The Evolution of the BHIVA Guidelines 2001-2014

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Setting the scene

Attitudes to Pregnancy Pre HAART

- Reproductive possibilities were much restricted in the first years of the HIV pandemic
  - Centers for Disease Control and Prevention (CDC) ***discouraged*** pregnancy in HIV-infected persons due to the poor prognosis of the disease and the risk of transmission to the neonate
  - American College of Obstetrics and Gynaecology, which recommended HIV-infected women ***not*** to become pregnant [1]
  - In 1994 the American Society for Reproductive Medicine suggested other ***alternative options*** such as donor insemination or child adoption
  - HIV-positive individuals continued to seek pregnancy, assuming the risk of sexual and/or vertical transmission of HIV [2]

1. Kass, et al, 1994. 2. Selwyn, et al. 1987

Attitudes to Pregnancy Post HAART

- In 2001 CDC revised their advice stating
  - "healthcare professionals should 'provide information and give support to any reproductive option for HIV-positive patients', particularly when HIV infection is under medical control"
- The growth in plans for pregnancy among HIV-infected individuals along the HAART era has been highlighted in many reports [1-5]
- In the UK, dedicated guidelines for
  - HIV in Pregnancy, 2001 [6]
  - Sexual and reproductive health, 2008 [6]

1. Riley and Yawetz, 2005. 2. Schuster, et al, 2000. 3. Chen, et al, 2004. 4. Klein, et al, 2003. 5. da Silveira, et al., 2005. 6. www.bhiva.org

Preconception advice

HIV +ve: Reproductive options 2001

HIV+ woman & HIV- man

- Insemination of partner's sperm at ovulation (whether or not on ARVs / detectable viral load)
- Assisted reproduction in case of fertility disorders
- Adoption

HIV+ man & HIV- woman

- IUI, IVF or ICSI following sperm washing (not available on NHS)
- Insemination of donor sperm at ovulation
- Adoption

HIV+ man & HIV+ woman

- Natural conception (if effective viral suppression) timed ovulatory intercourse only
- Insemination of sperm at ovulation
- Adoption

Treatment as Prevention

- Swiss statement 2008
- HPTN 052
- Partners in Prevention
- Partner Study

BASHH PEPSE Guidelines 2015

Table 4 Situations when post-exposure prophylaxis (PEP) is considered (IV, grade C)

	Source HIV status			
	HIV-positive		Unknown from high prevalence group/area*	Unknown from low prevalence group/area
	Viral load detectab			
Receptive anal sex	Recommend	Not recommended	Recommend	Not recommended
Insertive anal sex	Recommend		Consider†	Not recommended
Receptive vaginal sex	Recommend	Not recommended	Consider†	Not recommended
Insertive vaginal sex	Recommend	Not recommended	Consider†	Not recommended
Fellatio with ejaculation‡	Consider	Not recommended	Not recommended	Not recommended
Fellatio without ejaculation‡	Not recommended	Not recommended	Not recommended	Not recommended
Splash of semen into eye	Consider	Not recommended	Not recommended	Not recommended
Cunnilingus	Not recommended	Not recommended	Not recommended	Not recommended
Sharing of injecting equipment	Recommended	Not recommended	Consider	Not recommended
Human bite§	Not recommended	Not recommended	Not recommended	Not recommended
Needlestick from a discarded needle in the community			Not recommended	Not recommended

Not recommended

*High prevalence groups within this recommendation are those where there is a significant likelihood of the source individual being HIV-positive. Within the UK at present, this is likely to be men who have sex with men and individuals who have immigrated to the UK from areas of high HIV prevalence (particularly sub-Saharan Africa)
†More detailed knowledge of local prevalence of HIV within communities may change these recommendations from *consider* to *recommended* in areas of particularly high HIV prevalence
‡PEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another's oral cavity
§A bite is assumed to constitute breakage of the skin with passage of blood

factors PEPSE *should not* be prescribed when the exposure is an undetectable plasma viral load.[102] In light of this evidence

HIV +ve: Reproductive options 2015

HIV+ woman & HIV- man

- Treatment of woman to VL<40c/ml then UPSI
- PrEP-C
- Insemination of partner's sperm at ovulation (whether or not on ARVs / detectable viral load)
- Assisted reproduction in case of fertility disorders
- Adoption

HIV+ man & HIV- woman

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HIV+ man & HIV+ woman

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Antiretroviral Therapy

Principles of Treatment

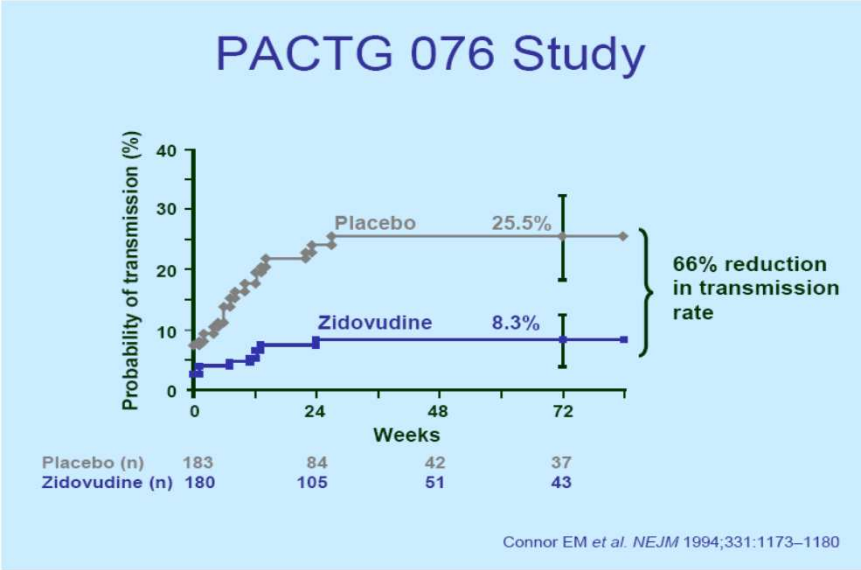
2001

- 15 compounds available
- Only Zidovudine specifically licensed
- Treatment may be stopped for first trimester!
- Antiviral pregnancy register started Jan 1989

Principles of Treatment

2001	2014
• 15 compounds available	• 32 compounds in use
• Only Zidovudine specifically licensed	
• Treatment may be stopped for first trimester!	
• Antiviral pregnancy register started Jan 1989	• Ongoing

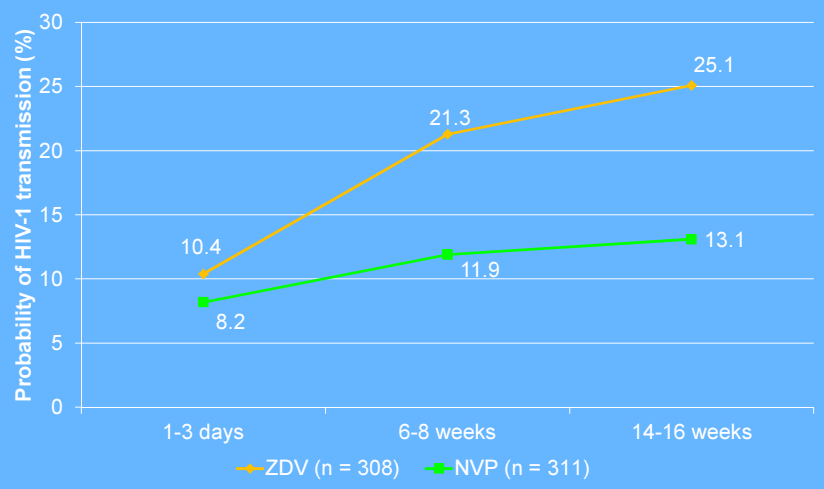
Monotherapy



PI Monotherapy

- Ritonavir 300mg BD increased to 600md BD
- MTCT rate 9.5%
- 10/86 discontinued because of hepatotoxicity

HIVNET 012: HIV transmission
Intrapartum/postpartum nevirapine vs zidovudine



Stat dose NVP for mother and infant vs ZDV for mother in labour and neonate 1/52

Adapted from Guay et al. Lancet 1999;354:795–802.

Dual Therapy

Dual Therapy

- AZT/3TC prospective non randomised study MTCT 2.6% but high rates resistance 15/132 (11%) if duration over 4 weeks
- Small studies showed higher resistance 80% when compared with ZDV mono
- Not recommended

Triple therapy/HAART/cART

Triple Therapy – PI based

2001

- MTCT 1.1% vs 7.8%
- Preterm delivery noted
- US cohort meta analysis ACTG 1998-99 PTD rate 20% but not attributable to a single drug class
- European data countered this
- Better if stopping therapy post delivery

Triple Therapy – PI based

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2014

- Preterm delivery an issue with PIs
- ATV/r less problematic than LPV/r
- More significant clinically in resource poor countries

Triple Therapy NNRTI based - NVP

2001

- NVP was added to mono, dual and triple therapy
- MTCT 1.5% vs predicted 5%
- But stopped study as could not discern what was best use of NVP
- Resistance 11% if VL >400c/ml at delivery

2014

- Still part of triple therapy
- Stepped down in BHIVA adult guidelines – no longer recommended or preferred

When to start therapy in pregnancy

2001

- Avoid first trimester – consider stopping!
- Consider avoiding D4t/DDI
- Switch Efavirenz
- Advised for woman's own health if CD4 200-350 cells/mm3
- Short Term Anti Retroviral Therapy

When to start therapy in pregnancy

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- Switch Efavirenz
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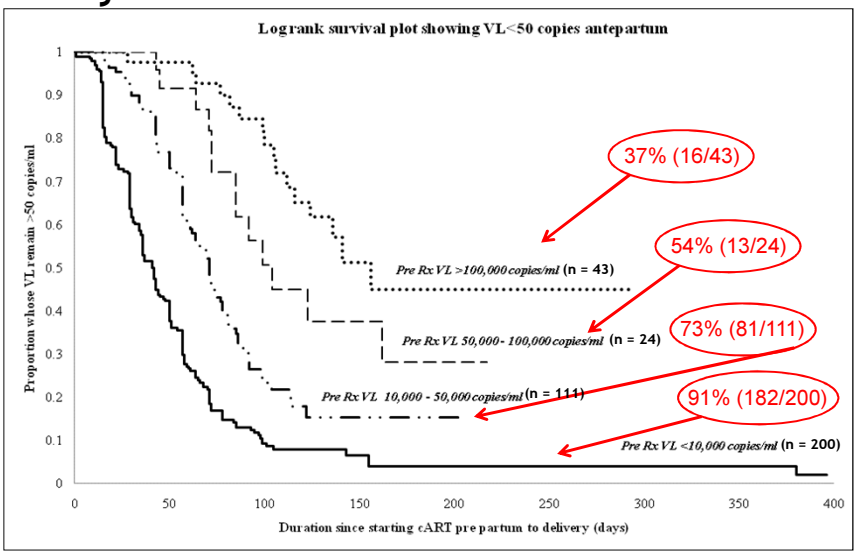
- Short Term Anti Retroviral Therapy

2014

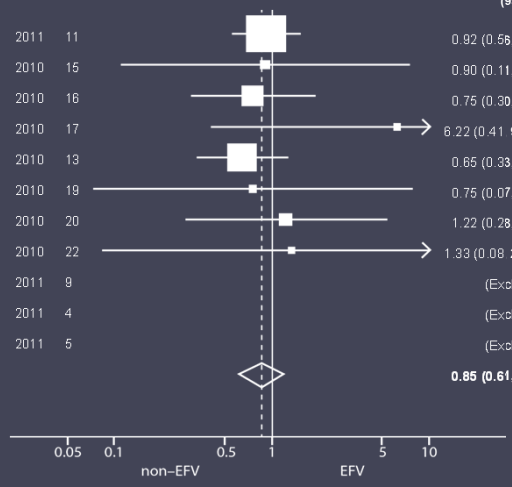
- Avoid first trimester if possible but VL guided
- D4t/DDI contraindicated
- Continue Efavirenz
- START trial means earlier CD4 count at initiation now recommended
- DO NOT STOP

Results: 77.2% overall undetectable at delivery



Read et al. AIDS 2011.

Relative risk of birth defects on efavirenz vs non-efavirenz regimens following first trimester exposure



Study	Year	Reference	Relative risk (95% CI)	Events/ Treatment	Events/ Control
Antiretroviral pregnancy register	2011	11	0.92 (0.56, 1.50)	17/623	147/4932
Bera *et al.*	2010	15	0.90 (0.11, 7.43)	5/184	1/33
Townsend *et al.*	2010	16	0.75 (0.30, 1.87)	5/204	48/1478
Machado *et al.*	2010	17	6.22 (0.41 95.10)	1/18	1/112
Gonzales-Tome *et al.*	2010	13	0.65 (0.33, 1.26)	7/31	93/266
Bussmann *et al.*	2010	19	0.75 (0.07, 7.78)	1/22	2/33
Floridia *et al.*	2010	20	1.22 (0.28, 5.31)	2/32	10/195
Patel *et al.*	2010	22	1.33 (0.08 21.51)	0/19	14/770
Ekouevi *et al.*	2011	9	(Excluded)	0/147	0/102
Phanupak *et al.*	2011	4	(Excluded)	0/6	0/180
Cressey *et al.*	2011	5	(Excluded)	0/4	0/21
Overall			**0.85 (0.61, 1.20)**	**38/1290**	**316/8122**

Ford *et al.* AIDS 2011, 25:2301–2304

START

Strategic Timing of Antiretroviral Treatment

A Multicenter Study of the International Network for Strategic Initiatives in Global HIV Research (INSIGHT)

START design

HIV positive people, ART-naïve with CD4+ count > 500

Early ART

Initiate ART immediately following randomization (N=2,000)

Deferred ART

Defer ART until the CD4+ count declines to < 350 or AIDS (N=2,000)

Follow until 370 endpoints reached

Primary endpoints

Table 1b. Relative rates of primary endpoints in each arm (15 May 2015)

	Rate per 100 PY		Hazard Ratio
	Early arm (A)	Late arm (B)	Arm A/B (95% CI)
Category 1:AIDS, serious non-AIDS, or death (primary).	0.60	1.25	0.47 (0.32 to 0.68)
Category 2:AIDS or AIDS death.	0.20	0.66	0.30 (0.17 to 0.55)
Category 3:Serious non-AIDS or non-AIDS death.	0.41	0.59	0.67 (0.42 to 1.09) NS **

* PY = patient years, ** NS = not statistically significant

Toxicity

2001
D4t/DDI – Lactic acidosis
NVP – rash/hepatotoxicity
RTV – hepatotoxicity
PI toxicity - gestational DM
PTD
Septrin – 1st trimester exposure causes NTD, cardiac and renal defects

Toxicity

2001	2014
D4t/DDI – Lactic acidosis	Contraindicated
NVP – rash/hepatotoxicity	CD4 guidance on starting
RTV – hepatotoxicity	Used only as a booster
PI toxicity - gestational DM	Same
PTD	PTD
Septrin – 1st trimester exposure causes NTD, cardiac and renal defects	Use increased dose folic acid to avoid toxicity

Mode of delivery

European mode of delivery study 1999

- **n=370, 1993–1998**
- **Randomised to vaginal delivery (VD) or elective caesarean section (ECS) at 38 weeks**
- **90% had CD4 >200**
- **65% took AZT during pregnancy**

HIV infected infants

PLCS	**3/170**	**1.8%**	***p*<0.001**
VD	**21/200**	**10.5%**	

- 0.8% transmission rate in women on AZT who had an elective CS

Shaw *et al*. *Lancet* 1999;353:1053-39

NSHPC

Very low risk of mother-to-child transmission of HIV in women on HAART achieving viral suppression in the UK and Ireland. Townsend, et al. *AIDS* 2008;22:973-981)

Mother-to-child transmission (MTCT) rates

	MTCT rate (%) 95% CI	n infected	Total
HAART	1.0 -	40	4120
HAART from conception	0.1 -	1	928
HAART + viral load <50 c/mL	0.1 (0.0–0.4)	3	2117

- 2 of the 3 had evidence of in utero infection

2 PLCS
1 SVD

Townsend *et al. AIDS* 2008;22:973–981

NSHPC

Very low risk of mother-to-child transmission ...iral ...end,

M... tr... ra...

...otal

HA... ...120

HA... ...28

HA... ...117

(0.0–0.4)

- 2 of the 3 had evidence of in utero infection

2 PLCS
1 SVD

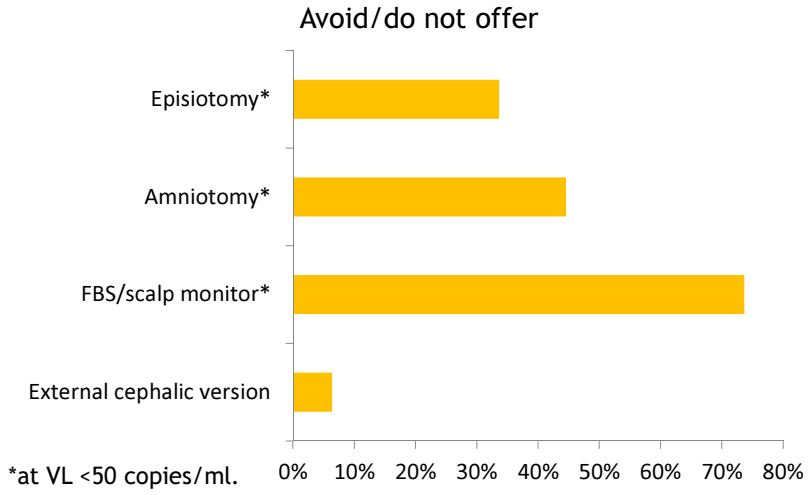
Townsend *et al. AIDS* 2008;22:973–981

- 2014
- For women with a plasma viral load of <50c/ml at 36 weeks, and in the absence of obstetric contraindications, a planned vaginal delivery is recommended
- Elite controllers on ART can aim for a NVD
- For women with a plasma viral load of 50-399 at 36 weeks, a pre-labour caesarean section (PLCS) should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views
- PLCS advised at 38-39 weeks to maximise fetal maturation

Invasive Obstetric procedures

BHIVA HIV in Pregnancy Audit 2014 Obstetric procedures

Guidelines: No evidence for avoiding these, treat as if HIV negative



*at VL <50 copies/ml.

Breastfeeding

Breastfeeding

- 1992: additional 14% risk[1]
- 1999 data re: 'exclusive' breastfeeding [2]
- 2001: formula feeding safe[3]
- 2005: favoured bottle feeding[4]
- Recent WHO revision following excess morbidity and mortality associated with early cessation of breastfeeding[5]

1. Dunn *et al. Lancet* 1992;340(8819):585-588. 2. Coudsoudis A *et al. Lancet* 1999;354(9177):471-6.
3 Mbori-Ngacha D *et al. JAMA.* 2001;286(19):2413-20. 4. Magoni M *et al. AIDS* 2005;19(4):433-7.
5. Bulletin of the World Health Organization 2008;86:210-214.

Mma Bana: Primary MTCT Endpoint

HIV Infections Among Live-Born Infants, n (%)	ZDV/3TC/ABC (n = 283)	ZDV/3TC + LPV/RTV (n = 270)	ZDV/3TC + NVP (n = 156)
In utero	3 (1.1)*	1 (0.4)	1 (0.6)
Intrapartum	0	0	0
Breastfeeding	2 (0.7%)	0	0
Total at 6 mos	**5 (1.8)***	**1 (0.4)**	**1 (0.6)**

* *P* = .NS for difference in between randomized arms.

- 1% overall transmission through 6 mos
  - 95% CI for overall MTCT rate = 0.5% to 2.0%

Shapiro R, et al. IAS 2009. Abstract WELBB101.

BHIVA Guidelines Amendment February 2010

- Exclusive formula feeding should still be recommended to all HIV-positive mothers in the UK
- Breastfeeding by women with detectable viraemia remains a safeguarding concern
- Women with fully suppressed HIV on ART, who choose to breastfeed should be supported to maximise adherence & encouraged to breast feed for the shortest time possible
- Monthly testing should be undertaken on mother (HIV RNA) and infant (HIV RNA or DNA) during breast feeding

Late presenting woman not on treatment 2001

- IV Zidovudine infusion
- Triple therapy for the infant

Late presenting woman not on treatment 2014

Late presenting woman not on treatment 2014

- A woman who presents after 28 weeks should commence HAART immediately based on the epidemiological incidence of resistance
- If her viral load is >100,000 c/ml or unknown, she should commence a 3 or 4 drug regimen to include Raltegravir
- A normal vaginal delivery is possible if a VL <50 copies/ml is achieved by 36 weeks

Late presenting woman not on treatment 2014

- An untreated woman presenting in labour at term should be given
  - a stat dose of nevirapine 200mg
  - commence fixed-dose zidovudine
  - with lamivudine and raltegravir
  - and have a continuous IV infusion of intravenous zidovudine for the duration of labour and delivery

World AIDS Day Number 1 2001 Blue

World AIDS Day Number 1 2014
Band Aid 30

Band AID 1984

BHIVA Guidelines HIV in Pregnancy Committee

2001

- Hermione Lyall
- Maggie Blott
- Annemiek de Ruiter
- David Hawkins
- Danielle Mercy
- Zuber Mitchla
- Marie-Louise Newell
- Siobhan O'Shea
- Richard Smith
- Judith Sunderland
- Ruth Webb
- Graham Taylor

2014

- Dr Annemiek de Ruiter
- Dr Graham ? Taylor
- Ms Polly Clayden
- Dr Jyoti Dhar
- Mrs Kate Gandhi
- Dr Yvonne Gilleece
- Dr Kate Harding
- Dr Phillip Hay
- Ms Jane Kennedy
- Dr Naomi Low-Beer
- Dr Hermione Lyall
- Dr Adrian Palfreeman
- Dr Siobhan O'Shea
- Dr Pat Tookey
- Ms Jennifer Tosswill
- Dr Steven Welch
- Dr Ed Wilkins

Evidence available BHIVA 2001

- RCTs or large meta analyses only available for
  - Formula Feeding
  - Pre-Labour Caesarean Section
  - Zidovudine monotherapy
- Relied heavily on expert opinion
- 170 references
- Mutlipdisciplinary authorship

BHIVA Guidelines 2014

- All evidence Graded
- 363 references
- Increased multidisciplinary authorship

Summary

- BHIVA HIV in Pregnancy guidelines have evolved using the increased evidence base on
  - ART efficacy in reducing MTCT
  - ART toxicity data
    - Studies
    - Antiviral pregnancy registry
  - Mode of delivery studies
  - Invasive Obstetric procedures
  - Breastfeeding studies
  - Late presenting woman

UCL

MTCT rates in diagnosed women, UK & Ireland 2000-2011

~12,500 singleton births; significant decline in MTCT over time ($p<0.001$)

Graph derived from data in Townsend *et al*. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. AIDS 2014; 28:1049–1057

National Study of HIV in Pregnancy and Childhood NSHPC

British HIV Association BHIVA

marking World AIDS Day

FHIVA federation of hiv associations

Prevention of Infant HIV Infection:
Aiming for zero transmission

A multidisciplinary conference for obstetricians, gynaecologists, HIV physicians and allied healthcare professionals

Friday 27 November 2015

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS
LONDON

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