HIV / hepatitis co-infection and prevention of vertical transmission

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BHIVA
British HIV Association

Competing interest disclosure

Relationships in previous 12 months

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Introduction

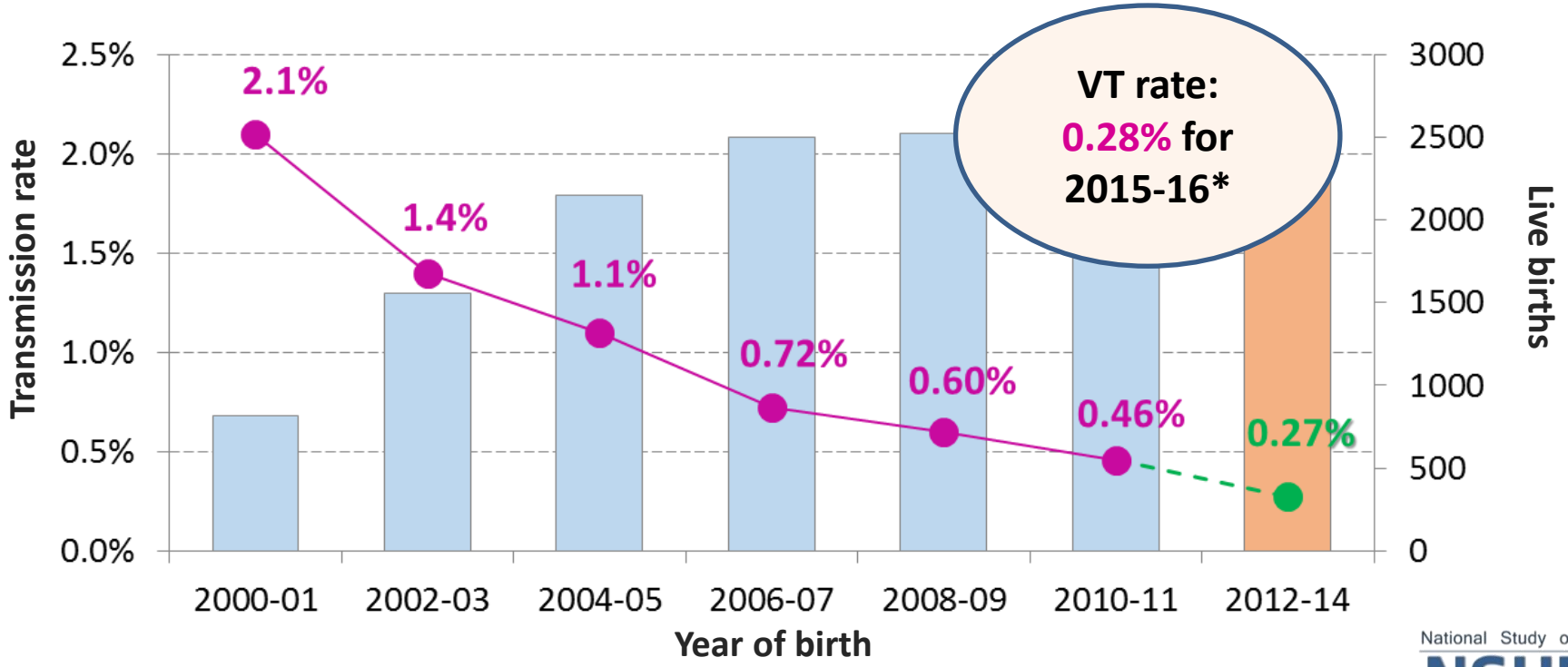
- HIV, HBV and HCV are leading global causes of mortality and morbidity
- Overlapping routes of acquisition for HIV and viral hepatitis means that co-infection is common
- Vast majority of children with these infections have acquired them vertically
  - On a global scale vertical transmission is the most important route for HBV
- All three viruses are the focus of specific global public health goals, e.g.
  - WHO: by 2030, to reduce new cases of chronic hepatitis B and C by 90%
  - UNAIDS Super Fast-Track Target of fewer than 20,000 new paediatric HIV infections by 2020; 90-90-90

Prevention of HIV vertical transmission

- Maternal HIV RNA load is the foremost risk factor for VT
  - Without any maternal ART 15-30% of formula-fed babies will become infected and up to 45% of those breastfed
- Suppressive ART in pregnancy and while breastfeeding is thus the main intervention to prevent VT
- In HICs, implementation of ART has reduced MTCT rates to <1-2% since ≈2000
- Coverage of ART in pregnancy in LMICs increased from 50% in 2010 to 75% in 2016
  - 47% reduction in new paediatric HIV infection over this period

UNAIDS 2018, Bailey et al 2018

Vertical transmission in UK/Ireland, 2000-2016



Data for 2000-11 from: Townsend *et al.* AIDS 2014; data for 2012-14 from Peters *et al.* CID 2016.
* data reported to NSHPC by end of March 2018

National Study of HIV in Pregnancy and Childhood

Pregnant women with HIV in the UK & Ireland Data for 2015-2016

National Study of HIV in
NSHPC
Pregnancy and Childhood

- 1914 singleton livebirths
- 71% deliveries in Black African women
- 17% deliveries to UK/Ireland-born women
- 70% pregnancies were conceived on ART
- **93% had delivery VL <50 (vs 87% in 2012-14)**

VTR

- Overall: **0.28%** (95% CI: 0.08%, 0.71%)
- Women diagnosed before conception with VL <50 throughout pregnancy: **0.17%** (95% CI: 0.01%, 0.92%)

Peters et al Int HIV Ped Workshop 2018

Vertical HIV transmission rates elsewhere in Europe

European Pregnancy & Paediatric HIV Cohort Collaboration

- Among women starting on ART in pregnancy in 2008-14
  - **VTR: 1.11%**
- Among all women in EU-based cohorts
  - **VTR: 0.7%** in 2012

French Perinatal Cohort, 2005-2015

- Among women on ART at conception (on LPV/r, ATZ/r, DRV/r or RAL), **VTR: <0.2%**

Russian Federation

- **VTR: 1.95%** (2016) and **1.7%** (2017, provisional data)

EPPICC IWHOD 2016, Sibiude et al CROI 2018, Favarato et al 2016, Latysheva 2018

Chronic hepatitis infection

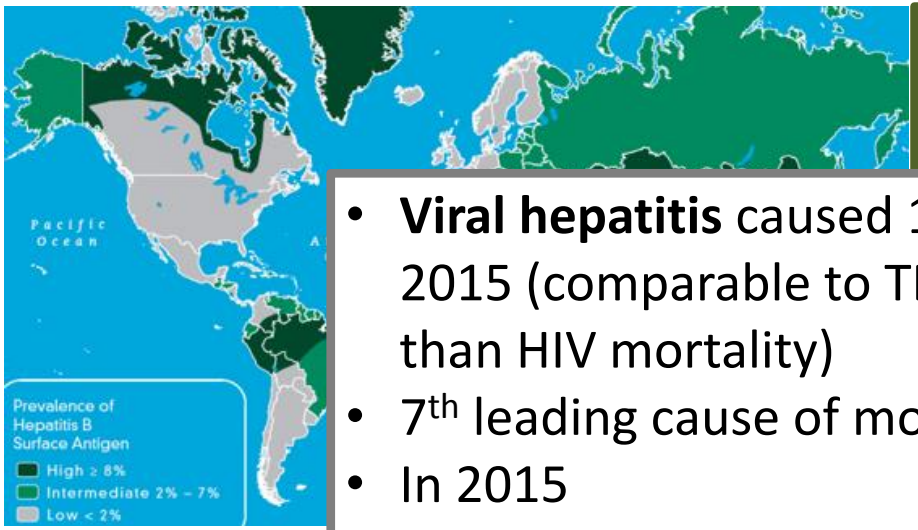
HBV

- **90%** of infected infants will become chronically infected versus **30-50%** of 1-4 year olds and **5-10%** of adults
- Adults with chronic HBV have a **15% lifetime risk** of death from cirrhosis or hepatocellular carcinoma

HCV

- **80-93%** of infected infants will become chronically infected, and around **70-85%** of infected adults
- Adults with chronic HCV: **15-20%** will develop liver cirrhosis after 20 years, and **1-5%** of those will progress to HCC annually

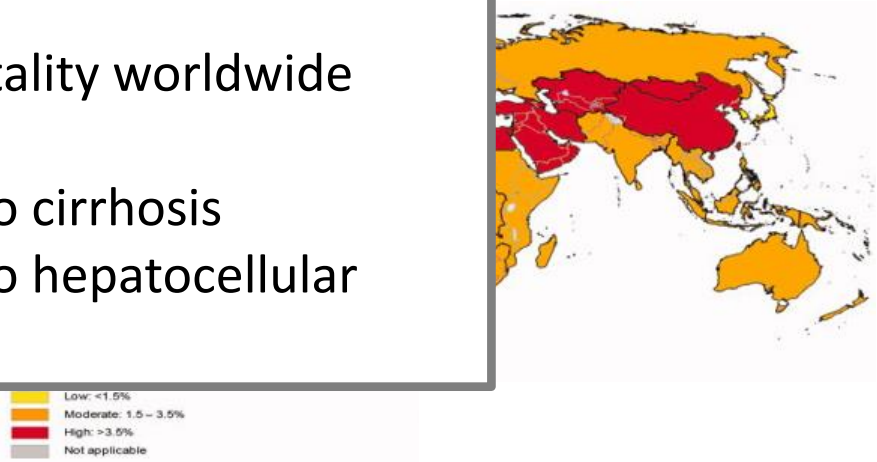
Global epidemiology of HBV & HCV



HBV
Globally, **257 million** people living with chronic HBV

- **Viral hepatitis** caused 1.34 million deaths in 2015 (comparable to TB mortality and higher than HIV mortality)
- 7th leading cause of mortality worldwide
- In 2015
  - 720 000 deaths due to cirrhosis
  - 470 000 deaths due to hepatocellular carcinoma

living with chronic HCV



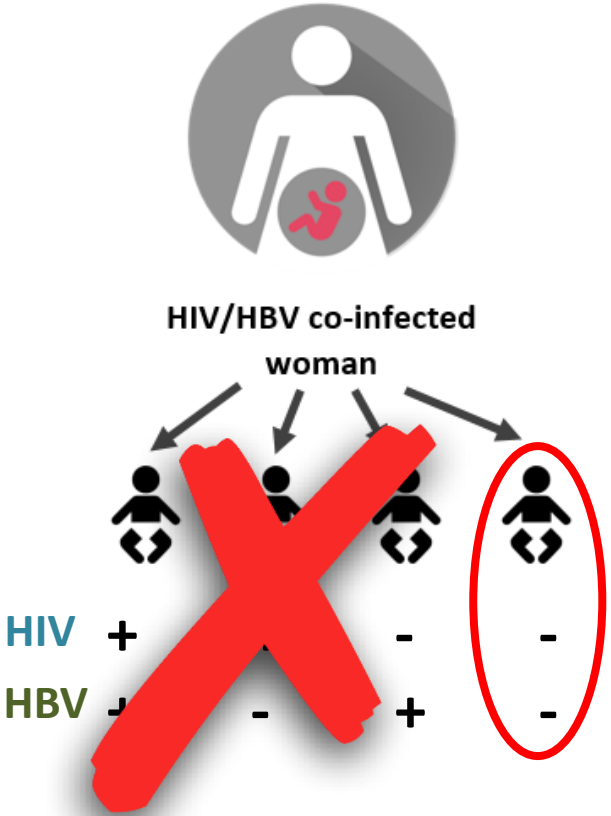
WHO Global Hepatitis Report 2017

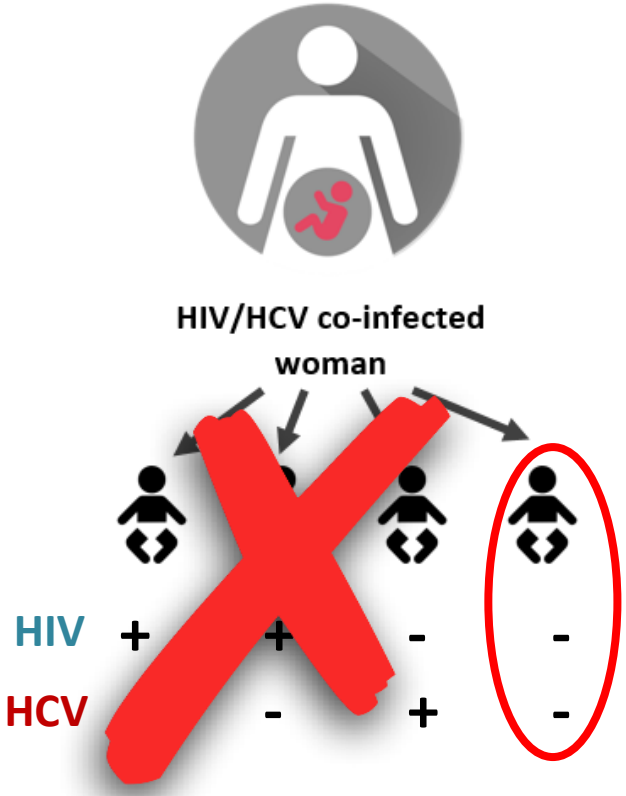
HIV and viral hepatitis co-infection

- Prevalence of chronic HBV and HCV in people living with HIV varies substantially by **region** and **within sub-populations**
- Estimated 5-20% of people living with HIV have **chronic HBV**
  - 20% in China, 10% in US, >20% in parts of Western Africa, 5% in UK
- 2% of people living with HIV have **chronic HCV** in the African region as a whole (but in some countries, this reaches 10-15%), whilst in UK 6% and in US 20% have HCV co-infection
- Among **people who inject drugs** who are HIV-infected, up to 90% may be **HCV** seropositive depending on setting

Singh et al 2017, Azevedo et al 2016, US Department of Health and Human Services 2016, Thornton et al 2017

Co-infections and vertical transmission





HBV vertical transmission

- Intrapartum transmission most important route, but *in utero* transmission can occur
- VT risk and immunoprophylaxis effectiveness (PEP with HBIG and vaccine) depends on maternal HBeAg status
- High maternal viral load (HBV DNA) increases ris
  - HBV DNA >10^7 IU/ml are at highest risk
- With appropriate immunop
  any additional risk of MTCT of HB

PEP with HBIG and complete vaccine schedule starting within 24 hours of life has 85-95% efficacy

	Vert	
	With no	Vacc
HBeAg positive	70-90%	5-10%
HBeAg negative	10-40%	<5%

Stevens et al 1985, Degli Esposti et al 2011; Chen et al 2013; Shi et al 2011; Lin et al 2014, Patton & Tran 2014; Zhang et al 2010; Lee et al 2006

HBV coinfection in pregnant women living with HIV

- 1.6% US (1998-2011)
- 2.1% Tshwane, South Africa (2008-2013)
- 3.1% Botswana (2010-2012)
- 5.0% Malawi (2004-2009)
- 9.3% Cameroon (2000-2003)
- 9.6% France (2000-2012)
- 12% Italy (2001-2016)
- 13% Thailand (2005-2007)
- 16.3% Temeke, Tanzania (2014)
- 17% Ukraine (2007-2012)

Salemi et al 2017; Diale et al 2016; Floridia et al 2017; Manyahi et al 2017; Bailey et al 2016; Chasela et al 2014; Mbangiwa et al 2018

HIV/HBV co-infection in the UK and Ireland

- Data from NSHPC: 2010-2016
  - Comprehensive surveillance in UK & Ireland
- **4.4% (95% CI 3.9, 4.8%) of pregnant women with HIV had chronic HBV**
  - Compares with HBsAg+ prevalence in England of ≈0.4% in general antenatal population (London ≈1.05%)
- Risk factors
  - Older maternal age
  - Born in sub-Saharan Africa

National Study of HIV in Pregnancy and Childhood
NSHPC

Peters et al NHIVNA 2017; Godbole et al 2013

Is there an increased risk of HBV co-infection in pregnant women living with HIV?

Setting	Higher prevalence in HIV-positive vs HIV-negative pregnant women?
South Africa	**5 fold** higher HBsAg prevalence
Tanzania	**2.5 fold** higher HBsAg prevalence
Botswana	**50%** higher HBsAg prevalence
Cameroon	Prevalence not increased
US	**8 times** increased risk of HBV co-infection, adjusting for age, ethnicity, substance use & hospital type

Data gaps

- Few data on HBeAg prevalence in HIV/HBV co-infected pregnant women
- African studies: 20-30%
- Thai study: 51%

- Practically no data on HBV viral load

Diale et al 2016; Salemi et al 2017; Manyahi et al 2017; Peters et al 2017; Kfutwah et al 2012; Rouet et al 2004; Mbangiwa et al 2018

Recommendations for preventing HBV vertical transmission

World Health Organization

All infants

- Use of HBV vaccination within 24 hours of birth for all (regardless of HBsAg status of mother)
- Completion of the HBV vaccine schedule within first year of life

For post-exposure prophylaxis

- HBIG as adjunct to above if feasible

Targets

- 90% childhood vaccine coverage by 2020
- 50% birth dose coverage or other PMTCT approach by 2020, 90% by 2030

Reasons for vertical HBV transmissions despite interventions

- High maternal viral load

World Health Organization March 2015

10.2: Prevention of mother-to-child HBV transmission using antiviral therapy	
	• In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.
Existing recommendations in HIV-infected pregnant and breastfeeding women[2]	• In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped. (*Strong recommendation, low to moderate quality of evidence*) [2] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

Efficacy of antivirals for preventing HBV VT

Pan et al RCT: 200 pregnant women in China, HBeAg+ and HBV DNA >200,000 IU/ml

- Randomised 1:1 to SoC without antiviral therapy, or TDF from 30-32 weeks gestation to 4 weeks postpartum
- All infants received immunoprophylaxis
- At delivery, 68% in TDF arm had HBV DNA <200,000 IU/ml vs 2% in control arm
- **VTR significantly lower in the TDF arm vs control arm** (ITT analysis: 5% vs 18%)

Meta-analysis

- 10 RCTs (all in China): average maternal baseline HBV DNA was 7.63 log10 IU/ml
- **Any antiviral vs. control reduced VT risk at 6-12 months** (HBsAg positivity: RR 0.3, 95% CI 0.2-0.4; HBV DNA positivity: RR 0.3, 95% CI 0.2-0.5)

Pan et al, NEJM 2016; Brown et al 2016

BHIVA guidelines: pregnant women with HIV/HBV

- Tenofovir-DF and emtricitabine or lamivudine backbone of ART in treatment-naïve women with wild type HIV/HBV
- If tenofovir-DF is not already part of ART, it should be added
- If clinical or genotypic evidence of lamivudine /emtricitabine resistant HBV or HIV then these may be omitted with tenofovir given as sole anti-HBV agent
- Emtricitabine is preferred option to be given with tenofovir
- First HBV vaccine dose with or without HBIG should start within 24 hours of delivery

BHIVA
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Vertical HBV transmission in HIV/HBV co-infection in the pre Option B+ era

Setting	MTCT Interventions	HBV MTCT (95% CI)
Thailand Khamduanget et al 2013 N=230	**Vaccine +/- HBIG** **No cART (sdNVP and ZDV only)**	**4.8%** **(2.4, 8.4%)**
Malawi BAN trial Chasela et al 2014 N=51	**Vaccine from 6 wks** **7 days 3TC+ZDV (mother and infant); maternal postnatal cART with 3TC for 28w in 1 of the 3 arms**	**9.8%** **(3.3, 21.4%)**

Vertical HBV transmission in HIV/HBV co-infection in the pre Option B+ era

Setting	MTCT Interventions	HBV MTCT (95% CI)
Thailand Khamduanget et al 2013 N=230	Vaccine +/- HBIG No cART (sdNVP and ZDV only)	4.8% (2.4, 8.4%)

93% uninfected

2.2% HIV infected (95% CI 0.7, 5.0)

4.8% HBV infected (95% CI 2.4, 8.4)

0% HIV/HBV co-infected (97.5% CI 1.6)

- 6.7% (2.9, 12.8%) among HBeAg positive and HBV DNA >6 log10
- 2.7% (0.6, 7.7%) among HBeAg negative

Vertical HBV transmission in HIV/HBV co-infection in the Treat All era

- Treating HIV/HBV co-infected pregnant women with a XTC+TDF-based regimen has potential to reduce VT, regardless of whether maternal HBV has been diagnosed
- No data yet to assess the impact of life-long ART with HBV-active drugs on VT of HBV in co-infected women in resource-rich or LMIC settings
- Consideration of HBV therapeutic benefit in future policy decisions regarding NRTI is needed, including recycling in second-line therapies

HCV vertical transmission

- Most (~70%) transmission occurs around time of delivery
- Rates of HCV vertical transmission from meta-analysis of 109 studies
  - HIV-negative mothers: **5.8%** (95% CI 4.2-7.8%)
  - HIV-positive mothers: **10.8%** (95% CI 7.6-15.2%)
- HCV viremia / high viral load is a risk factor, but not maternal genotype, mode of delivery or breastfeeding
- No interventions to prevent HCV vertical transmission <u>currently</u>
  - Exception: treating HIV in HIV/HCV co-infected women

Mok et al 2005, Benova et al 2014, Snijdewind et al 2014, Pembrey et al 2003

HCV seroprevalence in pregnant women living with HIV: outside Europe

- 1.5% Nigeria (2006-2011)
- 2.1% Uganda/Rwanda (2007)
- 3.0% Rwanda (2011)
- 3.7% Thailand (2000-2004)
- 4.8% Burkina Faso (2006)
- 2.8% United States (1998-2011)

Ezechi et al 2014 ; Simpore et al 2006; Pirillo et al 2007; Mutagoma et al 2017; Khamduang et al 2013; Salemi et al 2017

HCV seroprevalence in pregnant women living with HIV: Europe

- 2.7% France (2005-2013)
  - 1.7% chronic HCV (viremic)
- 13.7% Switzerland (2000-2014)
- 29% in 2000, 8% in 2008 Italy
- 33% Ukraine (2007-2012)
- St Petersburg, Russia
  - 70% (2004) and 50% (2008)
  - 88% in WWID and 24% of women who did not inject drugs
- 10% Irkutsk and 30% St Petersburg (EPPICC, 2013-15)

Floridia et al 2010; Kissin et al 2011; Bailey et al 2014; Aebi-Popp et al 2016; Benhammou et al 2018

HIV/HCV co-infection in the UK and Ireland

National Study of HIV in NSHPC Pregnancy and Childhood

- 2010-2016 data on diagnosed pregnant women with HIV
- **1.8%** (95% CI 1.5, 2.1%) had HCV co-infection (i.e. HCV seropositive)
- **Risk factors**
  - Younger maternal age - White ethnicity
  - Eastern European origin (30% of HIV/HCV+ from Eastern Europe)
  - History of injecting drugs (57% of women who inject drugs were HCV+)
- 10% of HIV/HCV co-infected women also had HBV co-infection
- No comparative national antenatal data, but estimates from a North Thames (2012) study in general antenatal population (neonatal DBS)
  - 0.095% HCV seropositive overall
  - By maternal area of birth: 0.37% Eastern Europe, 0.019% UK

Peters et al NHIVNA 2017; Cortina-Borja et al 2016

Vertical HCV transmission in HIV/HCV co-infection

Switzerland (MoCHiV) N=75

- 80% on ART at conception, 93% HIV VL <400 copies/ml at delivery
- **2.8%** (95% CI 0.3, 9.8) **HCV VTR**, no HIV transmissions

The Netherlands (ATHENA) N=24

- All on cART by delivery, 75% had HIV VL <500 copies/ml at delivery
- **4.2%** (95% CI 0.1, 24.1) **HCV VTR**, no HIV transmissions

France (EPF) N=68

- Around 50% women on ART at conception
- **5.9%** (95% CI 2.5, 10.4) **HCV VTR**, no HIV transmissions

Aebi-Popp et al 2016, Snijdewind et al 2015, Benhammou et al 2018

French data on adverse outcomes in pregnant women with HIV/HCV co-infection

- Compared 3902 HIV mono-infected women with 73 women with HIV and chronic HCV infection (i.e. viremic)
- **Cholestasis**
  - 13.9% versus 2.0% in HIV mono-infected women (aOR: 4.1 [95% CI 1.5, 10.8])
- **Preterm delivery**
  - 41.1% versus 15.2% in HIV mono-infected women (aOR: 3.0 [95% CI 1.6, 5.7])
- Findings **consistent with studies on HCV mono-infected women** and HIV/HCV co-infected (in Europe, US)
- Mechanisms need further research: may include HCV-related inflammation

Benhammou et al 2018; Baroncelli et al 2016; Ghazaryan et al 2016

HCV treatment in pregnancy?

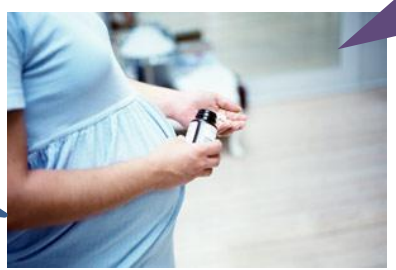
- Direct acting antivirals (DAA) for HCV treatment are potent, tolerable and efficacious
- Short duration of DAA regimen means that treating in the 3rd trimester might be an effective approach given that
  - most VT occurs at the end of pregnancy or during labour and delivery
  - HCV RNA levels decline precipitously once treatment is started
- Lack of human pregnancy data on DAAs; animal reproductive toxicity data available
- No DAA has approval for use in pregnancy currently
- Some DAAs show “promising” safety and PK profiles for potential use in pregnancy

Aebi-Popp et al 2016; Kanninen et al 2015; Spera et al 2016; Barrit & Jhaveri 2018

HCV treatment in pregnancy?

Double dividend – we can cure the mother and prevent HCV vertical transmission at the same time

If we treat woman BEFORE pregnancy then we can prevent fetal exposure to DAAs



But most pregnancies are unplanned

Why not wait until after delivery to treat the mother – and the baby if vertical transmission occurred?

What about postnatal loss to follow-up? In pregnancy we have an opportunity to treat while a woman is in touch with heath services

HCV treatment and pregnant women with HIV/HCV

- Most HIV/HCV co-infected women in the UK are diagnosed before pregnancy
- BHIVA guidelines recommend that women with HIV/HCV wishing to become pregnant should be prioritised for DAAs
- Increased all-cause and liver-related mortality among people living with HIV/HCV underscores need for treatment

Thornton et al 2017, BHIVA guidelines

DAAs in pregnancy: current studies

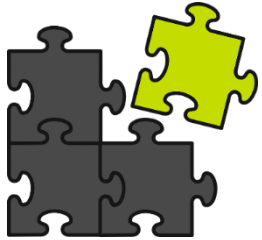
United States (Catherine Chappell, PI)

- Phase I PK and safety trial of Ledipasvir / Sofosbuvir (FDC)
- 15 women to be recruited
- GT1, 4, 5, 6
- HIV and HBsAg negative
- https://clinicaltrials.gov/ct2/show/NCT02683005

HCVAVERT (Judd, PI) – Europe, Egypt

- Trial development grant (2 years)
- Proposed trial on efficacy and safety of DAAs for HCV mono/HIV co-infected women from 3rd trimester to cure maternal HCV and prevent vertical transmission

HCV VT and prevention: knowledge gaps



- Timing of vertical transmission
- Safety of DAAs in pregnancy
- Potential cost-effectiveness of screening and treatment strategies in pregnancy
- Feasibility and acceptability of a DAA in pregnancy trial
  - Perception of and acceptability of level of HCV VT risk likely to vary
  - For a pregnant women living with HIV/HCV, a 5% HCV VTR may seem high given her HIV VTR risk on ART (<0.5%)

Prevention

- Prevent HBV and HCV infections in girls and women **living with and at risk of HIV infection**
  - Scale-up of HBV birth vaccination (60% of world's infants do not receive this currently)
  - Continue improvements in injection safety in medical settings
  - Harm reduction for people who inject drugs
- Diagnose, treat and cure HCV in HIV-co-infected girls and women prior to pregnancy

ELIMINATE ~~HEPATITIS~~

NOhep

Conclusion

- Burden of viral hepatitis/HIV co-infection varies by geographic setting and within sub-populations (e.g. high burden in WWID)
- There is substantial burden of hepatitis co-infection among pregnant women in some settings
- There remain gaps in knowledge around transmission risks and the public health impact of current strategies in context of HIV/Hep co-infection
- Research needed on risks, benefits and acceptability of DAAs in pregnancy
  - HCV treatment in pregnancy is a “compelling opportunity” (Barrit & Jhaveri 2018)
- Global targets of preventing new viral hepatitis cases will only be achieved if pregnancy and VT are given proper consideration

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