Safety of direct acting antivirals (DAA) to cure hepatitis C virus (HCV) in pregnancy 
And prevent VERTical transmission to the infant: HCVAVERT

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Risks and benefits of DAAs in pregnancy

(1) Cure the mother
(2) Prevent vertical transmission
(3) Adverse infant outcomes (birth defects, prematurity etc)

Hypothesis: Safety outcomes of DAA treatment of pregnant women with SOF/VEL during late 2\textsuperscript{nd}/3\textsuperscript{rd} trimester are non-inferior to current standard of care of no treatment of HCV during pregnancy. DAA treatment during pregnancy will prevent vertical transmission of HCV and cure the mother.
Phase II/III open-label 2 arm RCT

HCV PCR+ pregnant women randomised (2:1) at ≥24w gestation

A: Start SOF/VEL at ≥24wks gestation and before start of labour

B: No HCV treatment in pregnancy

Stratification by gestational age at enrolment (</≥35 weeks), country and HIV status

Follow up to birth for primary outcome and 6 months post-partum for secondary outcomes

PK curve in pregnancy

PK curve postpartum (BF)

Total sample size: n=510, of whom n=460 expected to present <35w
Primary and key secondary outcomes

Primary outcome (at birth)
• Congenital abnormalities
• Pre-term (≤37 weeks gestation)
• Pregnancy loss >24 weeks gestation
• Low birth weight (<2.5kg)

→ Non-inferiority of DAAs vs. no treatment in pregnancy
→ Primary analysis population: Women enrolled <35w gestation

Key secondary outcome (at 6 months post-partum)
• Vertical transmission i.e. proportion of infants who have a positive HCV RNA result by 6 months post-partum
Other secondary outcomes

- Maternal HCV cure (SVR12)
- Maternal and infant SAEs and grade 3 and 4 AEs
- All identified congenital abnormalities
- Infant growth and development
- Duration of breastfeeding
- Maternal quality of life
- Intervention arm: acceptability and adherence
Key inclusion criteria

- Pregnant ≥24 weeks gestation, not in labour
- ≥1 detectable HCV RNA within 60 days prior to enrolment
- HIV-, or if HIV+ then on ART compatible with SOF/VEL
- HBsAg-, or if HBsAg+, assessed for HBV viral load and HBV antiviral therapy
- Informed consent
Study sites

Pakistan
• Aga Khan University Hospital, Stadium Road, Karachi
• Aga Khan Maternal and Child Care Center, Hyderabad
• Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad
• Sheikh Zayed Hospital, Rahim Yar Khan

Ukraine
• ASTAR Medical Center, Lviv
• AIRMED Clinic, Odessa
• Kyiv City Centre of Reproductive and Perinatal Medicine

India
• PGIMER, Chandigarh
• Lady Hardinge Medical College (LHMC), Delhi
Substudies

- PK in 16 women
  - Pharmacokinetic curves in pregnancy, labour, breastfeeding
- Cost and cost-effectiveness
- Timing of vertical transmission
Need for an RCT on DAA use in pregnancy

• Recruitment across a range of setting with heterogeneous HCV epidemics → increase generalisability of results

• Control group important to distinguish impact of DAAs in pregnancy from consequences of HCV in pregnancy; randomised design reduces selection bias

• Large sample size will increase detection of adverse events

• Potential impact: contribute to international guidelines, move towards quadruple elimination of vertical transmission, increase choice for pregnant and breastfeeding women living with HCV in both HIC and LMIC
HCVAVERT trial team

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INSERM (health economics): Sylvie Deuffic-Burban

Netherlands:
PANNA (pharmacokinetics): Angela Colbers

Italy:
Penta Foundation: Carlo Giaquinto
University of Florence: Giuseppe Indolfi

PPI Partners: SALUS, Positive Women, The Health Foundation, CHAI, TAG, i-Base, WAVE (EACS)
Supporting partners: WHO, Pakistan MoH, UNICEF, CGHE
Pharmaceutical: Mylan (Viatris), Gilead