Teratogenicity in relation to Dolutegravir

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Outline

• Terminology
• What does it take to “make” a teratogen?
• Is DTG a teratogen yet?....the evidence so far
• How South Africa can contribute:
  • Teratovigilance Initiatives in South Africa
Terminology

• **Teratogen**
Anything that causes abnormalities in the development of the fetus if the mother is exposed to it during pregnancy e.g. chemicals, medications and infections (not all teratogens are medicines!)

• **Teratovigilance**
The aspects of teratology relating to understanding the epidemiology of teratogens and their impact on public health

• **Congenital Anomaly/Malformation/Disorder or Birth Defect**
Any structural or functional anomaly (e.g. metabolic disorder) that occurs during intrauterine life. (*not a single homogenous outcome!*)

“Teratogenesis is a unique kind of adverse drug effect, since it affects an organism (the fetus) other than the one for whom the drug was intended (the mother)....That “innocent bystander” status of the fetus raises profound medical, moral and legal issues.”

Allen A. Mitchell
in Pharmacoepidemiology, Strom et al, 2005
## Fetal effects not just malformations

<table>
<thead>
<tr>
<th>Effect</th>
<th>Examples of causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Abortion and Stillbirth</td>
<td>Maternal diabetes</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Major and minor anomalies</td>
<td>Phenytoin, sodium valproate, warfarin</td>
</tr>
<tr>
<td>Developmental problems</td>
<td>Sodium valproate, lead</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>cocaine</td>
</tr>
<tr>
<td>Cancer</td>
<td>Diethylstilboestrol</td>
</tr>
<tr>
<td>Social behaviour</td>
<td>Alcohol</td>
</tr>
</tbody>
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Adapted from slide by Prof Lewis B. Holmes
Assessing Causality...

Can the drug do it?

1. Pharmacology *(biologically plausible)*
2. Association in time *(gestational timing)* and place *(tissue of origin)* between exposure and event
3. Consistency of the association *(rechallenge / dose / class effect?)*
4. Specificity of the association - can event occur in absence of the exposure? *Confounding*
5. Data quality - malformation clearly described/diagnosed, timing of exposure, other exposures
6. Quantitative strength – dose and duration of exposure, effect size, study design, random error, bias
Shepard’s “Criteria for proof of human teratogenicity”

Consistent findings by two or more high quality epidemiological studies:

a) control of confounding factors;
b) sufficient numbers;
c) exclusion of positive and negative bias factors;
d) prospective studies, if possible;
e) relative risk of six or more (?).


Slide Acknowledgement – Professor Lewis Holmes
Special Characteristics of Teratovigilance

- Most pregnancies are unplanned – inadvertent exposures – women of child-bearing age (WOCBA) are at risk

- Teratogens do not uniformly increase rates of ALL congenital anomalies, but rather selected ones.

- Teratogenic risk is unknown for vast majority of medicines (poor data on biological plausibility) including OTC medicines

- Most teratogens do not cause a unique anomaly but rather cause increase in rate of known anomalies (e.g. neural tube defects (folic acid, other drugs). Cleft lip/palate, etc.)

- Some anomalies cannot be influenced by environmental exposures (e.g. chromosomal anomalies)

- Termination of pregnancy-abortion/stillbirth can avoid the outcome of interest if the outcome is only assessed in live-births
Large Sample Sizes Needed
Sample size estimation based on background incidence

<table>
<thead>
<tr>
<th>Incidence in Comparator Group</th>
<th>1 exposed/1 unexposed</th>
<th>1 exposed/4 unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR to be detected:</td>
<td>RR to be detected:</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Exposed</td>
<td>Exposed</td>
<td>Exposed</td>
</tr>
<tr>
<td>Unexposed</td>
<td>Unexposed</td>
<td>Unexposed</td>
</tr>
<tr>
<td>5%</td>
<td>474</td>
<td>474</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>274</td>
<td>1096</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>1%</td>
<td>2515</td>
<td>2515</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>1445</td>
<td>5780</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>244</td>
</tr>
<tr>
<td>0.1%</td>
<td>25471</td>
<td>25471</td>
</tr>
<tr>
<td></td>
<td>1272</td>
<td>1272</td>
</tr>
<tr>
<td></td>
<td>14621</td>
<td>58484</td>
</tr>
<tr>
<td></td>
<td>628</td>
<td>2512</td>
</tr>
</tbody>
</table>

Mehta U et al, BMC Pregnancy and Childbirth, 2012
Dolutegravir: Biological Plausibility & Consistency of Association

• **Animal data** *(FDA PI)*
  - Crosses placenta and excreted into breastmilk
  - Does not affect fertility in male or female rats/rabbits at 27x human dose
  - No evidence of developmental toxicity, teratogenicity or effect on reproductive function in rats and rabbits

• **Clinical trials**
  - 4 anomalies reported in 1 pharmacokinetic trial IMPAACT 1026s – later considered unrelated to DTG

• **Antiretroviral Pregnancy Registry***
  - 0 CNS effects reported as at 1 Jan 2018 - 3 anomalies reported from 133 preconception exposures (2.3%)

• **Other integrase inhibitors** – raltegravir – increase in supranuereal ribs in rat/rabbit at 3x human dose

*The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause; however, potential limitations of registries should be recognized. Providers are strongly encouraged to report eligible patients to SM_APR@INCREsearch.com or visit www.APRegistry.com.
Association in Time: Gestational Timing

FETAL DEVELOPMENT CHART

This chart shows vulnerability of the fetus to defects throughout 38 weeks of pregnancy.

* = Most common site of birth defects

Neural tube develops and closes by day 26 - 30 post fertilisation

Period of risk: Early first trimester

Exposures initiated after this period cannot be implicated (and haven’t been implicated)

LMP or gestational timing – often not known

https://www.cdc.gov/dotw/fasd/index.html

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https://www.cdc.gov/dotw/fasd/index.html
Data collection from 8 facilities across Botswana (45% of national birth cohort) Since 2014

Data collected at delivery from obstetric record including surface exam

In case of anomaly – study staff contacted to photograph anomaly after consent obtained

Photographs reviewed remotely by clinical geneticist -blinded to exposure

- TDF/FTC/DTG initiated as first line treatment in Botswana in 2016
- No increased risk of adverse birth outcomes among women initiated during pregnancy compared to TDF/FTC/EFV and no increased risk among 280 initiated during first trimester (Zash R, Lancet GH, 2018)
- Performed unplanned analysis in May 2018 for WHO Guidelines committee
- Signal of NTDs.....
89,064 births included in surveillance

88,755 births (99.7%) examined (live and stillbirths)

86 neural tube defects (0.1% of births; 95% confidence interval [CI], 0.08 to 0.12)

49 (57%) with photos

37 (43%) Confirmed by description (no photos)

42 meningocele or myelomeningocele, 30 anencephaly, 13 encephalocele, 1 iniencephaly.

Tsepamo Study: Botswana

Zash R et al, NEJM Sept 6 2018
Neural Tube Cases
1) Encephalocele
2) Anencephaly (no photo)
3) Myelomeningocele
4) Iniencephaly

Prevalence Difference by Exposure

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>4/426</th>
<th>14/11,300</th>
<th>3/5,787</th>
<th>0/2.812</th>
<th>61/66,057</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.94%</td>
<td>0.12%</td>
<td>0.05%</td>
<td>0.00%</td>
<td>0.09%</td>
</tr>
<tr>
<td>(0.37%, 2.4%)</td>
<td>(0.07%, 0.21%)</td>
<td>(0.02%, 0.15%)</td>
<td>(0.00%, 0.13%)</td>
<td>(0.07%, 0.12%)</td>
<td></td>
</tr>
<tr>
<td>Prevalence Difference</td>
<td>ref</td>
<td>-0.82%</td>
<td>-0.89%</td>
<td>-0.94%</td>
<td>-0.85%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.24%, -2.3%)</td>
<td>(-0.31%, -2.3%)</td>
<td>(-0.35%, -2.4%)</td>
<td>(-0.27%, -2.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Zash R, AIDS 2018
NEJM Sept 6, 2018
Tsepmo: Sensitivity Analysis & Update

• Sensitivity
  • No clustering in time (restricted analysis to rates after DTG introduction)
  • No clustering by facility
  • No change in case ascertainment (using postaxial polydactyly detection as marker)
  • No folate supplementation, epilepsy or diabetes prior to pregnancy in any cases

• Update analysis
  • July 2018- no new cases in T1 exposed DTG 4/596 (0.67%, 95% CI 0.26%-1.7%)
  • Next formal analysis – March 2019 – anticipate 1226 T1 exposures expanding to 18 facilities
  • “If only 1 more NTD case in total of 1226 – then lower CI will overlap with upper CI for other ART at conception”
Initiatives in South Africa

• SAHPRA - risk management plans
  • Acknowledgement of risk form for WOCBA
  • Companies required to support reporting to APR by clinicians who wish to contribute data on exposures.

• Pregnancy Exposure Registry /Birth Defect Surveillance (PER/BDS)
  • KZN – Durban South district - > 45 000 women to date – initiated Oct 2013
  • Western Cape – GMOU-MMH-GSH referral chain – initiated Sept 2016

• Conference: Building Teratovigilance Capacity in Africa - Nov 2017
  • [https://globalpharmacovigilance.tghn.org/resources/building-teratovigilance-capacity-africa/](https://globalpharmacovigilance.tghn.org/resources/building-teratovigilance-capacity-africa/)
WC PER/BDS Challenges

• Dependent on routine clinical data:
  • System strengthening – clinical examination & record keeping
  • Documenting drug histories
  • Documenting clinical examinations
  • Examination of stillborn infants

• Fetal autopsy

• Issue of infant identifiers (folder number) at MOUs & hospitals, esp. stillbirths: linkage

• Multiple patient identifiers

• PHCIS: operational database

• Accurate diagnosis of congenital disorders: photographs
Conclusion

• We are not yet certain that DTG is a teratogen
  • Need consistency of findings across studies
  • Bigger numbers – SA is ready to contribute

• Challenges in communicating risk-benefit in the presence of such uncertainty

• How to improve partnership with clients in decision-making?

• Require investment in robust post-marketing surveillance for pregnancy
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