Safety of Pediatric HIV Elimination: The Growing Population of HIV- and Antiretroviral-Exposed but Uninfected Infants

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One of the greatest public health successes has been the development and implementation of antiretroviral interventions to prevent mother-to-child HIV transmission (MTCT). The landmark 1994 Pediatric AIDS Clinical Trials Group (PACTG) 076 results, demonstrating zidovudine given to HIV-infected pregnant women and their infants reduced MTCT by nearly 70%, led to rapid implementation in the United States, with subsequent decline in MTCT from 25% to 4%-5% within two years [1]. Pregnant HIV-infected women in the United States and other high-resource countries now receive combination antiretroviral therapy (cART) including three or more drugs, which has led to further reductions in MTCT; in the United States, MTCT has been nearly eliminated, with rates currently <2% [2].

Additionally, there has been striking progress in reducing MTCT in resource-constrained countries, with 1 million children prevented from acquiring HIV between 2003 and 2013 because of maternal and infant antiretroviral prophylaxis [3]. The 2013 WHO consolidated guidelines recommend that all HIV-infected pregnant women initiate cART, and if breastfeeding, continue cART throughout breastfeeding [4]. After the MTCT risk period has ended, women may either continue life-long treatment regardless of clinical status or stop if they do not meet treatment eligibility criteria for non-pregnant individuals.

However, accompanying this success is a rapidly expanding population of HIV-exposed but uninfected children with substantial exposure to antiretroviral drugs, both in utero and, in resource-constrained countries, while breastfeeding. There is an urgent need to better understand the consequences of antiretroviral drug exposure on HIV-uninfected children and to improve monitoring and management of any potential adverse effects in this burgeoning population. Sibiude and colleagues in this week’s issue of PLOS Medicine provide a detailed analysis related to birth defects in infants with utero antiretroviral drug exposure in the French Perinatal Cohort [5].

Given the emphasis on early treatment of HIV in adults and the move toward initiation of lifelong therapy in all pregnant women in many resource-constrained countries, it can be anticipated that there will be a dramatic increase over time in women who conceive while receiving antiretroviral drugs, with fetal exposure from conception onward. Data from epidemiologic studies suggest MTCT may be lowest in infants born to mothers receiving cART prior to conception and continued during pregnancy [6]. However, there are only limited data on potential toxicities of fetal/infant antiretroviral drug exposure.

Birth Defects and Drug Exposures

A critical factor in the risk of drug-related birth defects is fetal developmental stage at the time of exposure. During the first two weeks after conception, exposures are unlikely to cause malformations, as immediately after conception the embryo has not yet formed, and after its formation, an additional period of time intervenes before its cells become committed to specific developmental paths [7]. The time of greatest sensitivity to teratogenic exposures is the stage of organogenesis (18–60 days after conception).
days after conception or 4–13 weeks after
the beginning of the last menstrual period),
before many pregnancies are recognized,
particularly in resource-constrained set-
tings. Exposures later in gestation are less
likely to produce gross structural abnor-
malities of the fetus. However, because this
period is a time of active cell growth,
differentiation, maturation, and migration,
particularly in the central nervous system
(CNS), teratogenic exposures may cause
growth retardation or functional CNS
disorders that may not be apparent until
much later in life and would be missed by
examination confined to the neonatal
period.

Animal studies have been used to
evaluate whether drug exposures may be
associated with teratogenic potential prior
to use in humans. However, it is difficult to
extrapolate animal findings because of
species differences in placentation, embryo-
conic development, innate predisposition to
fetal abnormalities, and drug pharmacoki-
etics/dynamics [7]. Thus, identification
of human teratogenic exposures relies
on epidemiologic studies, but such
studies require careful interpretation.
Ascertainment and recall biases can result
in erroneous associations. Additionally, the
maternal disease that created the need for
administration of the drug rather than the
drug itself could be responsible for an
observed association. Teratogenic expos-
ures most often produce distinct or
characteristic patterns of congenital ab-
normalities as opposed to a single malfor-
mation in an otherwise normal child [7].
Importantly, a statistically significant asso-
ciation in an epidemiologic study does not
necessarily indicate causality.

Birth Defects with Antiretroviral
Drug Exposure: French
Perinatal Cohort

The French Perinatal Cohort study
reports on defects detected at birth or within
a few days of birth, without extended
follow-up for later detection of birth defects,
and active fetal ultrasound surveillance was
not conducted.

The primary finding in the the French
Perinatal Cohort study was a significant
association of first-trimester zidovudine
exposure with congenital heart defects,
which persisted after adjustment for a
number of potential confounders. Most
were ventricular or atrial septal defects
(58% and 18%, respectively) and persist-
tent ductus arteriosus, and were not
associated with other malformations. The
clinical significance of these defects or
whether these were primarily detected
through active fetal ultrasound surveil-
ance was not described. Spontaneous
closure of ventricular septal defects (VSDs)
is frequent; in a study of 249 fetuses with
VSDs detected by fetal ultrasound, sponta-
nous closure of the VSD occurred in
5% of fetuses prenatally and 76% postna-
tally by age one year [9]. The association
of heart defects with first trimester zido-
udine exposure has been reported in two
smaller studies but not in larger cohorts,
including the Antiretroviral Pregnancy
Registry [8,10,11].

The authors also report a significant
association between first-trimester efavir-
enz exposure and neurologic defects in the
MACDP classification system of birth
defects, but not the EUROCAT classifi-
cation, which excludes minor anomalies
with no serious medical or functional
consequences [12]. Efavirenz-based
cART is the WHO recommended regi-
men for pregnant HIV-infected women;
primate data have raised concerns regard-
ing potential CNS teratogenicity
although data in humans have been more
reassuring [4,13]. The MACDP associa-
tion was based on only four CNS defects,
two of which (subependymal cyst and
partial agenesis of the corpus callosum)
are asymptomatic findings likely detected
on fetal ultrasound that may have no
clinical significance. None were neural
tube defects (a defect of concern from
primate studies) and they do not have
similar embryologic origins. Interestingly,
the three neural tube defects (spina bifida)
noted in live-births in the study were not
in efavirenz-exposed infants. While drug
exposure for the two neural tube defects
observed in pregnancy terminations was
not specified, since sensitivity analyses
including these defects were performed,
it is assumed these were also not in
efavirenz-exposed infants. Thus, these
data are actually reassuring regarding a
lack of neural tube defects in infants
with first-trimester efavirenz exposure
[5].

Reassuringly, no association with birth
defects were observed for other WHO-
recommended first or second-line drugs,
including tenofovir, lamivudine, and lopi-
avir/ritonavir [5].

Clinical Implications of the
French Perinatal Cohort Data

The use of antiretroviral drugs by HIV-
infected pregnant women has resulted in a
paradigm shift in the maternal and pediat-
ric HIV epidemics, with markedly im-
proved maternal survival and dramatic
reductions in MTCT. However, despite
the widespread use of antiretroviral drugs
by pregnant women, systematic evaluation
of birth defects has been limited. The
Antiretroviral Pregnancy Registry only
enrolls ~15% of HIV-infected pregnant
women giving birth annually in the United
States and only about 200 pregnant women
from other countries [8]; clinicians are
urged to report exposures to the Registry.

The largest amount of data on birth
defects and antiretroviral drug exposure
comes from high-resource countries.
However, the largest population of HIV-
infected women of childbearing age re-
sides in resource-constrained countries,
where women are exposed to multiple
factors that could increase risk of birth
defects, such as under-nutrition, micronu-
trient deficiency, anemia, and co-infec-
tions. Additionally, in many resource-
constrained countries, data on the back-
ground risk of birth defects in the general
population are lacking. Determining the
potential risk of birth defects due to
antiretroviral drug exposure requires
knowledge of the underlying risk of birth
defects in the population being studied.

Given that the HIV burden in women is
greatest in resource-constrained countries,
where rapid expansion in antiretroviral
drugs use in pregnancy (and increasingly
at conception) is expected with implemen-
tation of WHO guidelines, there is an
ethical imperative to systematically and
critically evaluate the safety of these
recommendations for the fetus/infant,
both in terms of potential teratogenicity
but also long-term outcomes. While the
Sibiu study raises some important ques-
tions, given the enormous benefits of
maternal antiretroviral drugs, the unclear
clinical significance of the heart defects
and the lack of a specific pattern of CNS
defects with efavirenz, no change in
prescribing practices is indicated, but
continued surveillance is critical.
WHO has established a Pregnancy Registry protocol that is beginning to be implemented in several resource-constrained countries [14]. Additionally, the President’s Emergency Plan for AIDS Relief (PEPFAR) is initiating active surveillance for birth defects in HIV-infected and uninfected women at sentinel sites in Malawi and Uganda. These data will be critical in evaluating safety of cART regimens and determining the best regimens to ensure the greatest benefit to the health of both the mother and her child.

Acknowledgments

The authors would like to thank George K. Siberry for his review and comments on an initial draft of this manuscript. Note: The findings and conclusions in this commentary are those of the authors and do not necessarily represent the views of the National Institutes of Health, State Department or United States government.

Author Contributions

Wrote the first draft of the manuscript: LM. Contributed to the writing of the manuscript: LM HW. ICMJE criteria for authorship read and met: LM HW. Agree with manuscript results and conclusions: LM HW.

References

1. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pit J, et al. (2002) Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J AIDS 29: 484–494.
2. Nesheim S, Harris LF, Lampe M. (2013) Elimination of perinatal HIV infection in the USA and other high-income countries: achievements and challenges. Curr Opin HIVAIDS 8: 447–456.
3. The United States President’s Emergency Plan for AIDS Relief. PEPFAR Tenth Annual Report To Congress (2014). See URL http://www.pepfar.gov/documents/organization/223065.pdf.
4. World Health Organization (2013) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Available: http://www.who.int/hIV/pub/guidelines/arc2013/download/en/index.html
5. Sibua J, Mandelbrot L, Blanche S, Le Chenadec J, Boullagoule N, et al. (2014) Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the ANRS CO1/CO11 French Perinatal Cohort Study. PLoS Med 11: e1001635.
6. Townsend CL, Byrne L, Cortina-Borja M, Thorne C, de Ruiter A, et al. (2014) Earlier initiation of ART and futher decline in mother-to-child HIV transmission rates, 2000–2011. AIDS 28: 1049–57.
7. Polifka JE, Friedman JM. (1999) Clinical teratology: identifying teratogenic risks in humans. Clin Genet 56: 409–420.
8. Antiretroviral Pregnancy Registry Steering Committee (2013). Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989–31 July 2013. Wilmington (North Carolina): Registry Coordinating Center. Available: http://www.APRegistry.com.
9. Gomez O, Martinez JM, Olivella A, Bennasar M, Cripi F, et al. (2014) Isolated ventricular septal defects in the era of advanced fetal echocardiography: risk of chromosomal anomalies and spontaneous closure rate from diagnosis to age of 1 year. Ultrasound Obstet Gynecol 43: 65–71.
10. Brogly SB, Abzug MJ, Watts DH, Cunningham CK, Williams PL, et al. (2010) Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trial protocols 219 and 219C. Pediatr Infect Dis J 29: 721–727.
11. Wam DH, Huang S, Culnane M, Kaiser KA, Scheneke A, et al. (2011) Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. J Perinat Med 39: 163–170.
12. Boyd PA, Haesler M, Barisic I, Loane M, Garne E, et al. (2011) Paper 1: The EUROCAT network – organization and processes. Birth Defects Res A Clin Mol Teratol 91 Suppl 1: S2–S15.
13. Ford N, Calmy A, Mofenson L (2011) Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 25: 2301–2304.
14. Mehta U, Clerc K, Allen E, Yore M, Sevne E, et al. (2012) Protocol for a drugs exposure pregnancy registry implementation in resource limited settings. BMC Pregnancy Childbirth 12: 89.