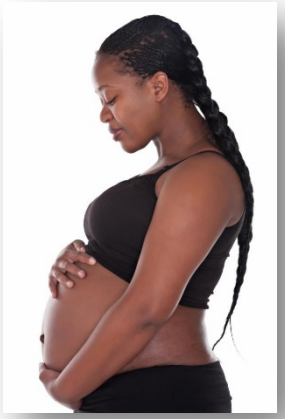
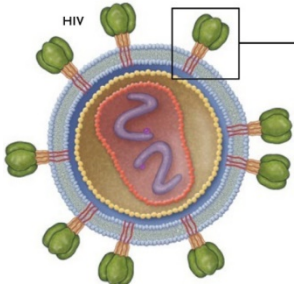
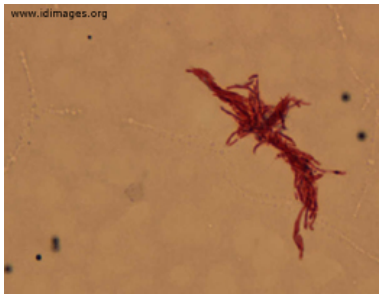
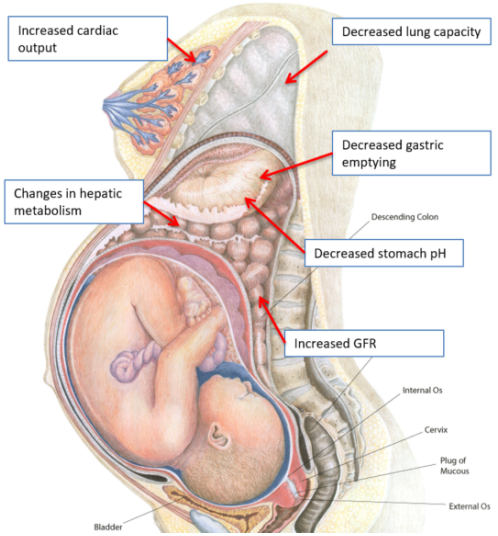








Historic Perspective on HIV and TB Research in Pregnant Women

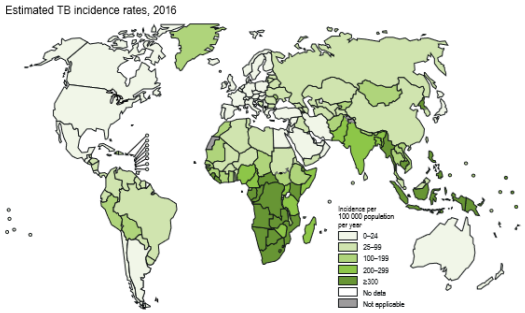
Lynne M. Mofenson, M.D.
Senior HIV Technical Advisor
Elizabeth Glaser Pediatric AIDS Foundation

Elizabeth Glaser Pediatric AIDS Foundation

Until no child has AIDS.

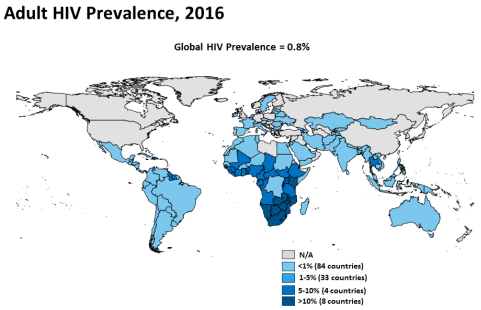
High Burden of TB/HIV in Women - 2016

TB

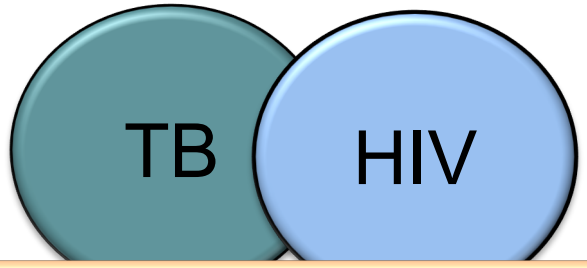


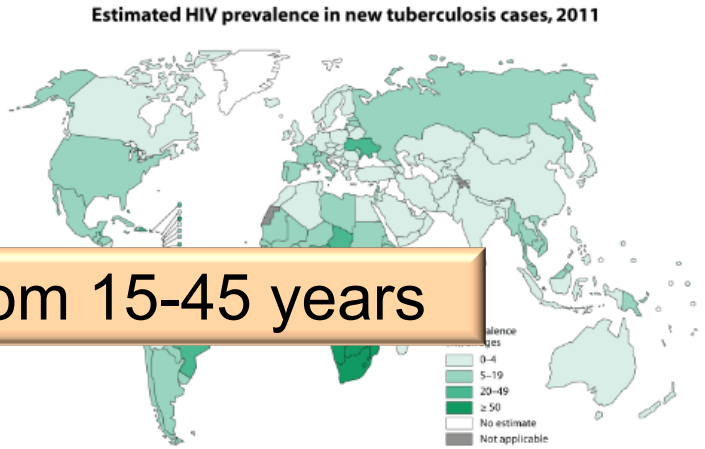
- 10.4 million new cases
- Women
  - 3.2 million new cases (35%)
  - Deaths 493,000
  - Pregnant: est. 216,500 (2011)

HIV



- 1.8 million new cases
- Women
  - 900,000 new cases (50%)
  - Deaths 850,000
  - Pregnant: est. 1.1 million





Highest burden in reproductive age from 15-45 years

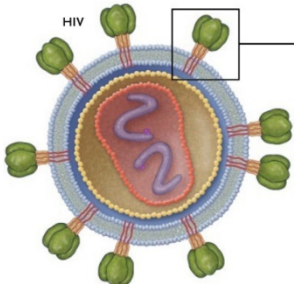
WHO Global TB Report 2017, UNAIDS Global AIDS Report 2016
Sugarman J et al. Lancet Glob Health 2014

Considerations About Drug Use in Pregnancy

- **HIV and TB**
  - We know both HIV and TB associated with significant morbidity and mortality for the pregnant woman and her fetus/infant.
  - There are approved drugs, most have animal reproductive toxicity data but *limited data in humans*.
  - Data for *some* drugs on placenta/breast milk passage in humans, but only in animals for others.
  - **OTHER BIG UNKNOWNS:**
    - Pharmacokinetics and safety in pregnancy.
    - Optimal time to start (can it be used in 1st trimester?).
    - Benefits and risks in pregnancy.

Take-Away Message

- The lack of data on drugs needed to treat important illnesses such as HIV and TB in pregnant and breastfeeding women – and when studied, the long period it takes to obtain such data after a drug is first approved – was and remains unacceptable.



HIV and Drugs in Pregnancy

Historically, initial focus was on prevention of mother-to-child HIV transmission and not so much on maternal health

HIV Treatment Era Begins in 1987

- AZT approved by FDA March 1987 for treatment of adults based on efficacy in persons with AIDS/ARC.

The New England Journal of Medicine

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Volume 317 JULY 23, 1987 Number 4

THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D.PHIL., DANNIE KING, PH.D., AND THE AZT COLLABORATIVE WORKING GROUP

- Significant hematologic toxicity; severe anemia/neutropenia (24%/16%); 21% required blood transfusion.

THE TOXICITY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

DOUGLAS D. RICHMAN, M.D., MARGARET A. FISCHL, M.D., MICHAEL H. GRIECO, M.D., J.D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., MARTIN S. HIRSCH, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D.PHIL., SANDRA NUSINOFF-LEHRMAN, M.D., AND THE AZT COLLABORATIVE WORKING GROUP

- Only 4.8% those enrolled in trial were female; pregnancy contraindication to enrollment, so there were no data in pregnancy.

We Did Have Some Preclinical & Reproductive Toxicity Data - with Some Potential Concerns

- Carcinogenic in rodents at but only at high doses (mice 3x, rats 24x human levels).
- No teratogenicity rats/rabbits.
- Transplacental carcinogenicity in mice – AZT given in high doses to pregnant mice associated with tumors in offspring:
  - *Study 1:* AZT ~3x human exposure to pregnant mice and offspring X 24 mo: ↑ vaginal tumors offspring
  - *Study 2:* AZT high dose (450 or 1000 mg/kg) to pregnant mice only: ↑ tumors in lung, liver, & female reproductive tracts in the offspring at highest AZT dose

1990: Potential Use of AZT to Prevent HIV Mother-to-Child Transmission?

- Given availability of AZT, association of MTCT with viral load, and the high mortality of pediatric AIDS, pediatric & obstetric researchers proposed giving AZT to infected pregnant women to reduce MTCT.
- However, giving a potentially toxic drug to pregnant women and exposing their fetuses was highly controversial.

Zidovudine (AZT) (Retrovir) kills

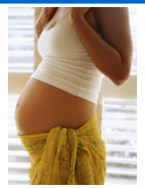
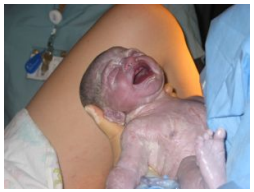
WARNINGS AND PRECAUTIONS
Hematologic toxicity/bone marrow suppression including neutropenia and severe anemia
Symptomatic myopathy associated with prolonged use of zidovudine.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases,
(package insert note)

www.carlg.org

- FDA held public meeting on ethics of giving AZT to pregnant women and whether the 076 clinical trial should be allowed to proceed.

PACTG 076: AZT Regimen Targeted Multiple Potential Time Points of Transmission

CD4 >200

Pregnancy	Labor/Delivery	Infant
		
AZT 100 mg 5 times daily	AZT IV 2 mg/kg 1 mg/kg/hr	AZT 2 mg/kg q 6 hr x 6 weeks
TARGET: *In Utero* (after 1st trimester)	TARGET: Intrapartum	TARGET: Postpartum
	Pre-Exposure Prophylaxis (PrEP)	**Post-Exposure Prophylaxis (PEP)**

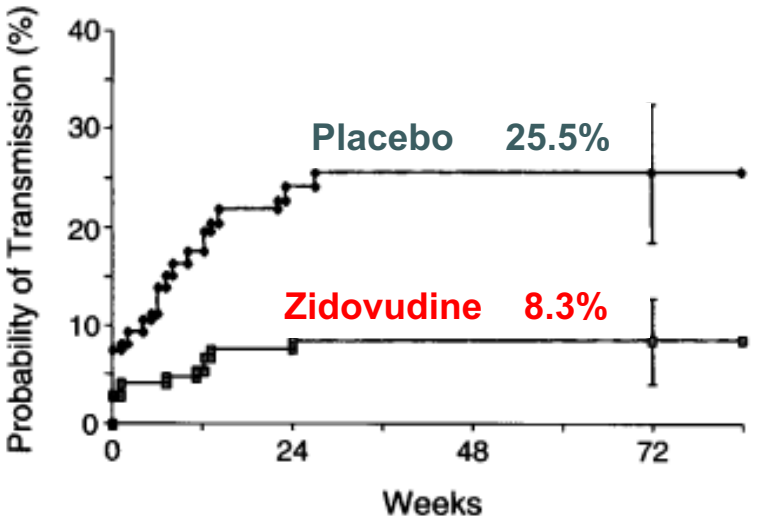
DSMB halted trial Feb 1994

The New England Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

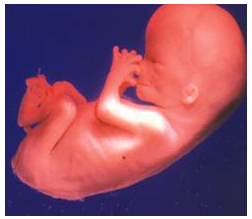
Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Moye, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D.,
for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*



→ Led to paradigm shift in use of ARV drugs in pregnancy

Given Recommendations for Antiretroviral Treatment in Pregnancy, Need for Systematic Data Collection on Short- & Long-Term Effects of Exposure

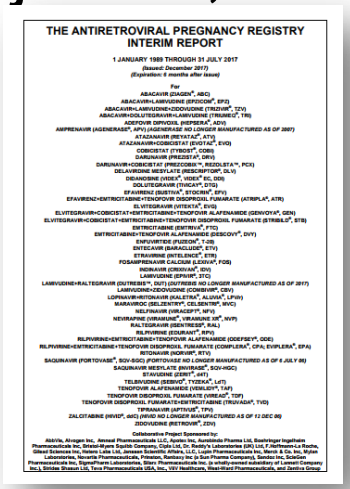
Fetal exposure raises issues related to potential short-term (pregnancy outcome, birth defects) and long-term (e.g., transplacental carcinogenicity) outcomes



The Antiretroviral Pregnancy Registry

Birth Defect Surveillance: Antiretroviral Pregnancy Registry

- 1990: Glaxo starts *Zidovudine in Pregnancy Registry*, building on Acyclovir in Pregnancy Registry.
  - Independent advisory committee, semi-annual public report
  - Early warning signal of major teratogenicity; estimates risk of major birth defects compared to general population
- 1993, other pharmaceutical manufacturers of ARV joined, became *Antiretroviral Pregnancy Registry*.


THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT

1 JANUARY 1989 THROUGH 31 JULY 2017

(Issued: December 2017)
(Expiration: 6 months after issue)

For

ABACAVIR (ZIAGEN®, ABC)
ABACAVIR+LAMIVUDINE (EPZICOM®, EPZ)
ABACAVIR+LAMIVUDINE+ZIDOVUDINE (TRIZIVIR®, TZV)
ABACAVIR+DOLUTEGRAVIR+LAMIVUDINE (TRIUMEQ®, TRI)
ADEFOVIR DIPIVOXIL (HEPSERA®, ADV)
AMPRENAVIR (AGENERASE®, APV) (AGENERASE NO LONGER MANUFACTURED AS OF 2007)
ATAZANAVIR (REYATAZ®, ATV)
ATAZANAVIR+COBICISTAT (EVOTAZ®, EVO)
COBICISTAT (TYBOST®, COB)
DARUNAVIR (PREZISTA®, DRV)
DARUNAVIR+COBICISTAT (PREZCOBIX™, REZOLSTA™, PCX)
DELAVIRDINE MESYLATE (RESCRIPTOR®, DLV)
DIDANOSINE (VIDEX®, VIDEX® EC, DDI)
DOLUTEGRAVIR (TIVICAY®, DTG)
EFAVIRENZ (SUSTIVA®, STOCRIN®, EFV)
EFAVIRENZ+EMTRICITABINE+TENOFOVIR DISOPROXIL FUMARATE (ATRIPLA®, ATR)
ELVITEGRAVIR (VITEKTA®, EVG)
ELVITEGRAVIR+COBICISTAT+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (GENVOYA®, GEN)
ELVITEGRAVIR+COBICISTAT+EMTRICITABINE+TENOFOVIR DISOPROXIL FUMARATE (STRIBILD®, STB)
EMTRICITABINE (EMTRIVA®, FTC)
EMTRICITABINE+TENOFOVIR ALAFENAMIDE (DESCOVY®, DVY)
ENFUVIRTIDE (FUZEON®, T-20)
ENTECAVIR (BARACLUDE®, ETV)
ETRAVIRINE (INTELENCE®, ETR)
FOSAMPRENAVIR CALCIUM (LEXIVA®, FOS)
INDINAVIR (CRIXIVAN®, IDV)
LAMIVUDINE (EPIVIR®, 3TC)
LAMIVUDINE+RALTEGRAVIR (DUTREBIS™, DUT) (DUTREBIS NO LONGER MANUFACTURED AS OF 2017)
LAMIVUDINE+ZIDOVUDINE (COMBIVIR®, CBV)
LOPINAVIR+RITONAVIR (KALETRA®, ALUVIA®, LPV/r)
MARAVIROC (SELZENTRY®, CELSENTRI®, MVC)
NELFINAVIR (VIRACEPT®, NFV)
NEVIRAPINE (VIRAMUNE®, VIRAMUNE XR®, NVP)
RALTEGRAVIR (ISENTRESS®, RAL)
RILPIVIRINE (EDURANT®, RPV)
RILPIVIRINE+EMTRICITABINE+TENOFOVIR ALAFENAMIDE (ODEFSEY®, ODE)
RILPIVIRINE+EMTRICITABINE+TENOFOVIR DISOPROXIL FUMARATE (COMPLERA®, CPA; EVIPLERA®, EPA)
RITONAVIR (NORVIR®, RTV)
SAQUINAVIR (FORTOVASE®, SQV-SGC) (FORTOVASE NO LONGER MANUFACTURED AS OF 6 JULY 06)
SAQUINAVIR MESYLATE (INVIRASE®, SQV-HGC)
STAVUDINE (ZERIT®, d4T)
TELBIVUDINE (SEBIVO®, TYZEKA®, LdT)
TENOFOVIR ALAFENAMIDE (VEMLIDY®, TAF)
TENOFOVIR DISOPROXIL FUMARATE (VIREAD®, TDF)
TENOFOVIR DISOPROXIL FUMARATE+EMTRICITABINE (TRUVADA®, TVD)
TIPRANAVIR (APTIVUS®, TPV)
ZALCITABINE (HIVID®, ddC) (HIVID NO LONGER MANUFACTURED AS OF 12 DEC 06)
ZIDOVUDINE (RETROVIR®, ZDV)

Collaborative Project Sponsored by:

AbbVie, Alvogen Inc., Amneal Pharmaceuticals LLC, Apotex Inc, Aurobindo Pharma Ltd, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Cipla Ltd, Dr. Reddy's Laboratories (UK) Ltd, F.Hoffmann-La Roche, Gilead Sciences Inc, Hetero Labs Ltd, Janssen Scientific Affairs, LLC, Lupin Pharmaceuticals Inc, Merck & Co. Inc, Mylan Pharmaceuticals Inc, Sandoz Inc, Shionogi Inc, Strides Pharma Inc, Sun Pharmaceutical Industries Ltd, Teva Pharmaceuticals USA, Inc, ViiV Healthcare, West-Ward Pharmaceuticals, and Zentiva Group

- Currently international registry including 120 antiretroviral drugs – 48 brand, 72 generic drugs

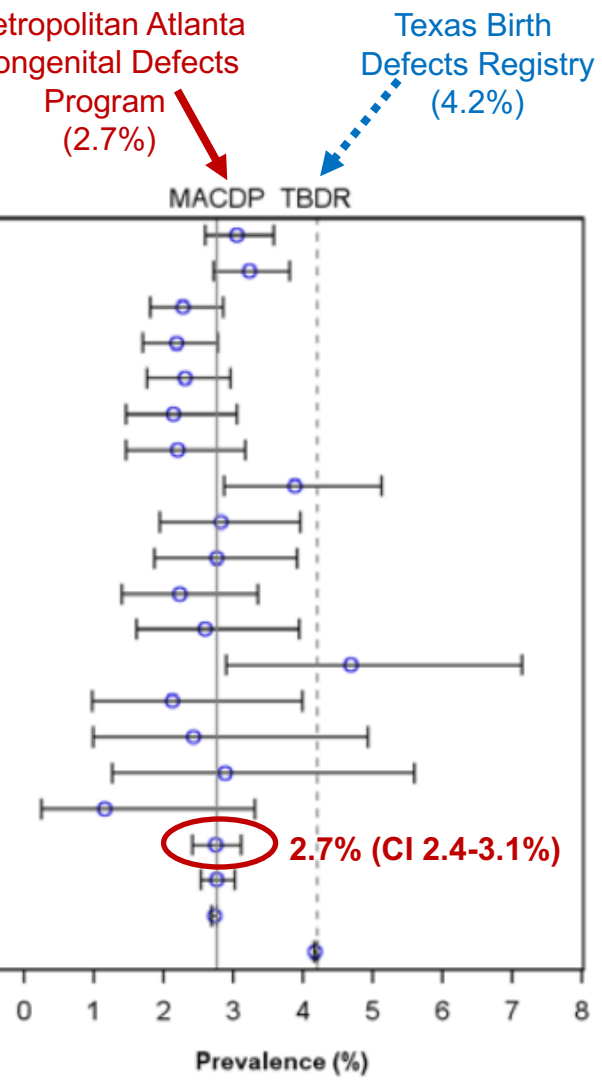
Drug-Specific Birth Defect Rates*

Prevalence of Birth Defects (95% CI): 1 January 1989 – 31 January 2017
First Trimester Exposure

*For drugs meeting threshold of ≥ 200 1st trimester exposed pregnancies

1 January 1989 through 31Jul2017

	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	149/4880	3.05	2.59	3.58
Zidovudine	134/4160	3.22	2.71	3.80
Tenofovir DF	76/3342	2.27	1.80	2.84
Ritonavir	67/3071	2.18	1.69	2.76
Emtricitabine	60/2614	2.30	1.76	2.95
Lopinavir	30/1400	2.14	1.45	3.05
Atazanavir	27/1235	2.19	1.45	3.17
Nelfinavir	47/1212	3.88	2.86	5.12
Nevirapine	32/1135	2.82	1.94	3.96
Abacavir	30/1088	2.76	1.87	3.91
Efavirenz	22/990	2.22	1.40	3.35
Stavudine	21/811	2.59	1.61	3.93
Didanosine	20/427	4.68	2.88	7.14
Darunavir	9/425	2.12	0.97	3.98
Indinavir	7/289	2.42	0.98	4.93
Raltegravir	8/278	2.88	1.25	5.59
Rilpivirine	3/263	1.14	0.24	3.30
First Trimester APR	244/8909	2.74	2.41	3.10
Any Trimester APR	501/18129	2.76	2.53	3.01
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19



MACDP: Metropolitan Atlanta Congenital Defects Program
TBDR: Texas Birth Defects Registry

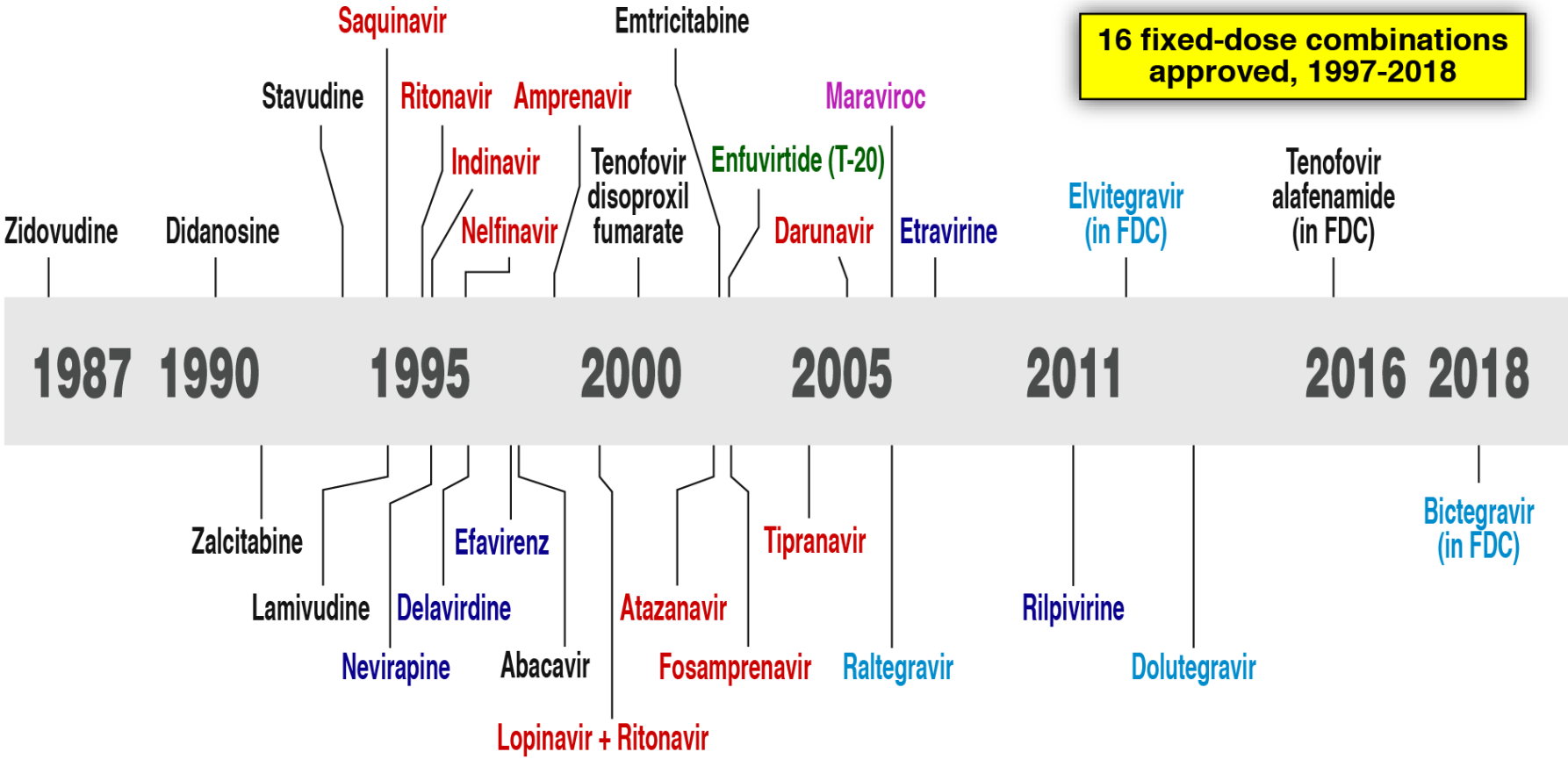
Long-Term Adverse Effects Will Require Special Epidemiologic Studies

pHACS
Pediatric HIV/AIDS Cohort Study

SMARTT
Surveillance Monitoring for Antiretroviral Treatment Toxicity

- Pediatric HIV/AIDS Cohort Study:
  - NIH-funded study following HIV-exposed and antiretroviral-exposed but uninfected (HEU) children into adolescence and beyond.
  - Screens multiple organ system domains, with trigger-based evaluation if abnormality is identified.

Antiretroviral Drugs Approved by FDA, 1987-2018



NNRTIs (5)
NRTIs (8)
Fusion Inhibitor (1)
Protease Inhibitors (9)
Entry Inhibitor (1)
Integrase Inhibitors (4)
Pharmacokinetic Enhancers (2) - not shown

Source: FDA

- Of the 30 ARVs approved in adults, only **one** (AZT) has indication in pregnancy (for PMTCT).
- Generally, drug label language is *"use only if potential benefit exceeds potential risk"* and prohibits use during breastfeeding.

VIDEX EC- didanosine capsule, delayed release
Bristol-Myers Squibb Company

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving didanosine.

VIREAD- tenofovir disoproxil fumarate tablet, coated
VIREAD- tenofovir disoproxil fumarate powder
Gilead Sciences, Inc.

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response VIREAD should be used during pregnancy only if clearly needed.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving VIREAD.

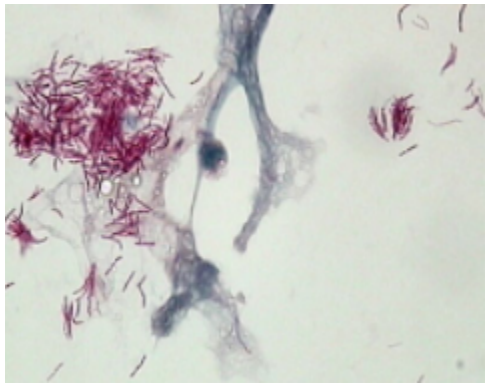
Antiretroviral Drug Approvals Adults/Data in Pregnancy

- Search PubMed "x drug and pregnancy"

	Year FDA approved in adults	1st publication of data in pregnancy
NRTI/NtRTI (9 counting TDF and TAF separately)		
ABC	1998	2004 (abstract) **+ 8 Years**
AZT	1987	1991 **+ 4 Years**
ddI	1991	1999 **+ 8 Years**
FTC	2003	2009 **+ 6 Years**
3TC	1995	1998 **+ 3 Years**
ddC	1992	**NO DATA**
d4T	1995	2003 (abstract) **+ 8 Years**
TAF	2015	**NO DATA**
TDF	2001	2009 **+ 8 Years**
NNRTI (5)		
EFV	1998	2008 **+ 10 Years**
DLV	1997	**NO DATA**
ETV	2008	2011 **+ 3 Years**
NVP	1996	1998 (dose labor) **+ 2 Years**
RPV	2011	2014 **+ 3 Years**

	Year FDA approved in adults	1st publication of data in pregnancy
Protease inhibitors (9)		
ATV	2003	2007 **+ 4 Years**
DRV	2006	2010 **+ 4 Years**
F-APV	2003	2013 **+ 10 Years**
IDV	*2004*	*2003 (pre-approval)*
LPV/r	2000	2004 (abstract) **+ 4 Years**
NFV	1997	2000 (abstract) **+ 3 Years**
RTV	1996	2002 (abstract) **+ 6 Years**
SQV	1995	2001 **+ 7 Years**
TPV	2005	2008 **+ 3 Years**
Entry & Fusion Inhibitors (2)		
T20	2003	2008 **+ 5 Years**
MVC	2007	2015 **+ 6 Years**
Integrase Inhibitors (4)		
BIC	Feb 7 2018	**NO DATA**
DTG	2013	2016 **+ 3 Years**
EVG	2012	2016 **+ 4 Years**
RAL	2007	2012 **+ 5 Years**
Pharmacologic Boosters (2 counting RTV)		
COBI	2015	2016 **+ 1 Year**

→Mean delay between FDA approval and pregnancy data was **5 years**



TB and Drugs in Pregnancy

Nguyen et al. BMC Infectious Diseases 2014, 14:617
http://www.biomedcentral.com/1471-2334/14/617

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Tuberculosis care for pregnant women: a systematic review

Hang Thanh Nguyen[1*], Chiara Pandolfini[1], Peter Chiodini[2] and Maurizio Bonati[1]

Paucity of Studies on TB Drugs in Pregnancy

- Systematic review of papers on "tuberculosis and pregnancy" to evaluate studies focusing on TB care for pregnant women up through 2012.

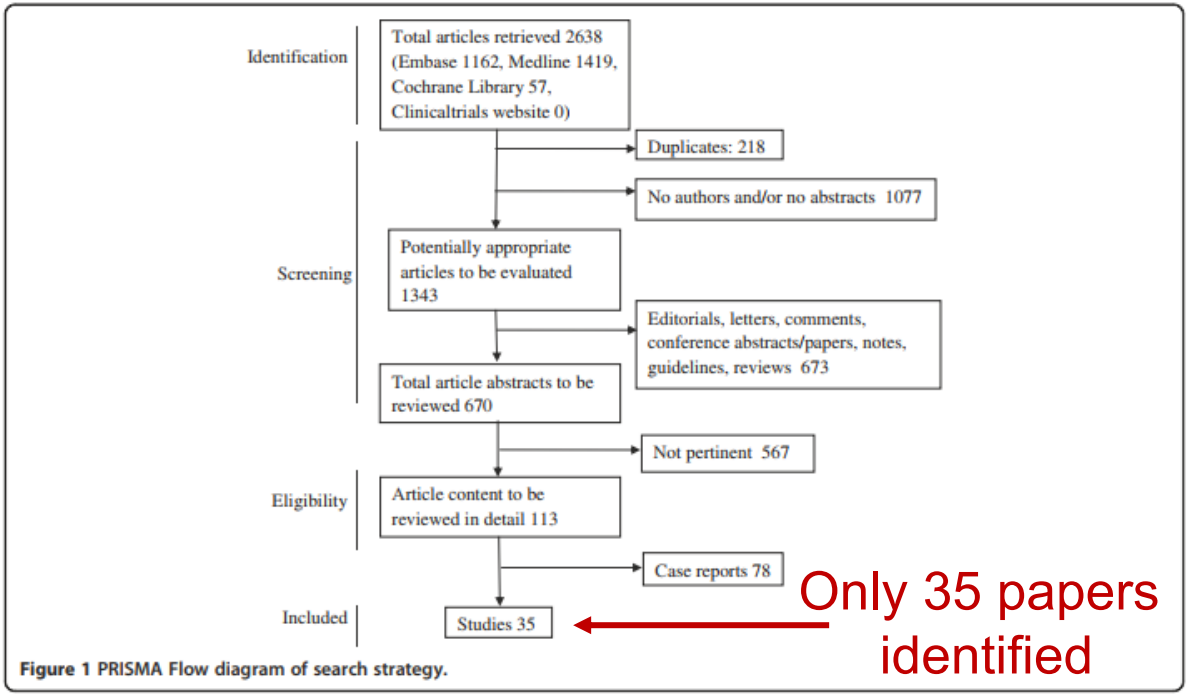
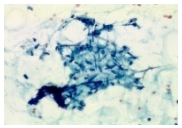


Figure 1 PRISMA Flow diagram of search strategy.

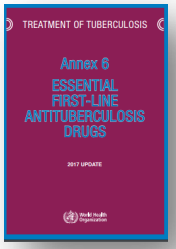
For TB treatment: there were 375 pregnant women with TB in **14 studies**, including 4 studies in 55 women with MDR TB



TB in Pregnancy

- Data on safety, tolerability, and pharmacokinetics of TB drugs during pregnancy have not been reported systematically, leading to inconsistencies in national and international treatment guidelines.
- For example, WHO recommends use of pyrazinamide during pregnancy in 1st line TB therapy but CDC does not, owing to inadequate data on potential adverse fetal effects.

WHO



Pregnancy and breastfeeding

With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy: streptomycin is ototoxic to the fetus and should not be used during pregnancy.

Use in pregnancy

The 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible. Although detailed teratogenicity data are not available, pyrazinamide can probably be used safely during pregnancy.

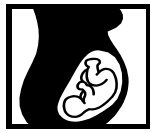
CDC

TB Treatment and Pregnancy

TB Disease

- The preferred initial treatment regimen is INH, rifampin (RIF), and ethambutol (EMB) daily for 2 months, followed by INH and RIF daily, or twice weekly for 7 months (for a total of 9 months of treatment).
- Streptomycin should not be used because it has been shown to have harmful effects on the fetus.
- Pyrazinamide (PZA) is not recommended to be used because its effect on the fetus is unknown.

First-Line TB Drugs and Pregnancy



- Because of the lack of studies in pregnancy, first-line tuberculosis drugs were all listed as former US FDA "Pregnancy Category C" (i.e., no adequate well-controlled human studies have been performed, but benefits may be acceptable despite potential risks).

Drug Name	FDA Category[a]	WHO Group[b]	Crosses Placenta (cord: maternal ratio)	Fetal Toxicity	Breastfeeding Compatible	Teratogenic in Reproductive Toxicity Studies	Concerns in Pregnancy and Postpartum
Isoniazid	C	1	Yes	CNS defects	Yes	No	Possible hepatotoxicity
Rifampin	C	1	Yes	Hemorrhage	Yes (minimal passage)	Yes[c]	Possible postpartum hemorrhage; interacts with NNRTIs, PIs, decreases efficacy of hormonal contraceptives
Ethambutol	C	1	Yes	Jaundice	UD (minimal passage)	Yes (low incidence)	. . .
Pyrazinamide	C	1	UD	Jaundice	UD (excreted in breast milk)	UD	. . .

UD= Undetermined *(despite many years of use of these drugs)*

☐ = teratogenicity in animal repro studies *(but no way to systematically collect data on TB drugs in human pregnancy)*

Gupta A et al. Clin Infect Dis 2016;62:761-9

Multi-Drug Resistant (MDR) TB in Pregnancy

- MDR TB presents special challenge, because treatment options remain extremely limited as pregnant women are excluded from most new TB drug trials.

Eight Ongoing or Planned Phase 3 and 4 TB Treatment-Shortening Trials

Trial[a]	TB Type	Drugs in Regimens Under Study	Pregnant Women
NIX-TB (NCT02333799)	XDR	BDQ, LZD, Pa	No
NEXT (NCT02454205)	MDR	BDQ, LZD, LFX, PYZ, ± HD INH or ETO	No
TB-PRACTECAL (NCT02589782)	MDR/XDR	BDQ, LZD, Pa, ± MFX or CFZ	No
STREAM II (NCT02409290)	MDR	CFZ, ETO, MFX, PYZ, INH, KAN, PTO, CFZ, ETO, MFX, PYZ, INH, PTO, BDQ, CFZ, ETO, MFX, PYZ, INH, KAN, PTO, BDQ	No
STAND (NCT02342886)	DS	Pa, MFX, PYZ	No
TBTC Study 31 (NCT02410772)	DS	INH, PYZ, HD RPT, ± MFX or ETO	No
TRUNCATE-TB	DS	INH, PYZ, HD RIF, E, ± CFZ or LZD, INH, PYZ, RPT, LZD, LFX, INH, PYZ, ETO, LZD, BDQ, INH, PYZ, LZD, LFX, DLM	No
endTB	MDR	CFZ, DLM, MFX, PYZ, CFZ, BDQ, LFX, LZD, PYZ, CFZ, DLM, LFX, LZD, PYZ, BDQ, LZD, MFX, PYZ, BDQ, DLM, LZD, LFX, PYZ	No

Abbreviations: BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid; DS-TB, drug-sensitive tuberculosis; E, ethambutol; ETO, ethionamide; HD, high dose; INH, isoniazid; KAN, kanamycin; LFX, levofloxacin; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; MFX, moxifloxacin; Pa, pretomanid; PTO, protionamide; PYZ, pyrazinamide, RIF, rifampin; RPT, rifapentine; TBTC, Tuberculosis Trials Consortium; XDR-TB, extensively drug-resistant tuberculosis.

[a]National Institutes of Health clinical trial identifiers are shown; for more information, go to ClinicalTrials.gov.

McKenna L et al. Clin Infect Dis. 2017;65:1383-7

Multi-Drug Resistant (MDR) TB in Pregnancy

- Most aminoglycosides – which have been key for MDR treatment - are potentially ototoxic and nephrotoxic for the fetus; reproductive toxicity studies suggest other 2nd line drugs, such as ethionamide-prothionamide, may have teratogenic potential.
- There are new compounds in development and new oral drugs approved for MDR TB treatment in the US (bedaquiline) and Europe (bedaquiline and delamanid), **but lack of safety or PK data during pregnancy severely limits use in this population**.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 62 / No. 9
October 25, 2013

Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis

Bedaquiline may be used on a case-by-case basis in children, HIV-infected persons, pregnant women, persons with extrapulmonary MDR TB, and patients with comorbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided.

Quality of evidence: insufficient.

Expert opinion: The possible benefits of using bedaquiline outweigh the potential risk.

Evidence basis and rationale: The effectiveness and safety of bedaquiline for the treatment of MDR TB have not been studied adequately in these populations to provide general guidance for or against its use. Because MDR TB has a high mortality rate and treatment options are limited, its use might be a reasonable option for providers to consider in treating certain patients in the groups listed above.

MDR TB Drugs and Pregnancy

Drug Name	FDA Category[a]	WHO Group[b]	Crosses Placenta (cord: maternal ratio)	Fetal Toxicity	Breastfeeding Compatible	Teratogenic in Reproductive Toxicity Studies	Concerns in Pregnancy and Postpartum
Aminoglycosides							
Capreomycin	C	2	Yes	. . .	UD	Yes[d]	. . .
Streptomycin	D	2	Yes	Ototoxicity, thrush, diarrhea	Yes (minimal passage)	No	. . .
Kanamycin	D	2	Yes	Ototoxicity	Yes (minimal passage)	No	. . .
Amikacin	D	2	Yes	. . .	UD	UD	. . .
Levofloxacin	C	3	Yes	. . .	Yes	No[e]	. . .
Moxifloxacin	C	3	Yes	. . .	UD	No[e]	. . .
Gatifloxacin	C	3	UD	. . .	UD	No	. . .
Ethionamide/ Prothionamide	C	4	UD	Developmental anomalies	UD	Yes	Developmental abnormalities in human case series
P-aminosalicylic acid	C	4	UD	Diarrhea	No	No	. . .
Cycloserine	C	4	UD	. . .	Yes	UD	Congenital sideroblastic anemia
Terizidone	. . .	4	UD	. . .	UD	UD	. . .
Thiacetazone	. . .	5	UD	. . .	UD	UD	. . .
Clofazimine	C	5	UD	Reversible skin pigmentation	UD	No	. . .
Clarithromycin	C	5	Yes (0.15)	. . .	UD	No[f]	. . .
Amoxicillin- clavulanic acid	B	5	Yes (0.56)	Necrotizing enterocolitis, transaminitis	UD	No	. . .
Linezolid	C	5	UD	. . .	UD	No	. . .
Imipenem	C	5	UD	. . .	UD	No	. . .
Rifabutin	B	. . .	UD	. . .	UD	No	. . .
High-dose isoniazid	C	. . .	Yes (0.73)	CNS Defects	UD	No[g]	Possible hepatotoxicity
Bedaquiline	B	. . .	UD	. . .	UD[h]	No	Drug accumulation in tissues
Rifapentine	C	. . .	UD	. . .	UD	Yes[i]	Possible postpartum hemorrhage; interacts with NNRTIs, PIs, may decrease efficacy of hormonal oral contraceptives
Delamanid	Not Approved[j]	. . .	UD	. . .	UD	Yes[j]	Embryofetal toxicity at maternally toxic doses in rabbits; breast milk concentration 4 times higher than blood in rats

UD= Undetermined

Gupta A et al. Clin Infect Dis 2016;62:761-9

Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Clinical Infectious Diseases® 2016;62(6):761–9

Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel

Amita Gupta,[1,a] Jyoti S. Mathad,[8,a] Susan M. Abdel-Rahman,[9] Jessica D. Albano,[10] Radu Botgros,[18] Vikki Brown,[11] Renee S. Browning,[3] Liza Dawson,[3] Kelly E. Dooley,[2] Devasena Gnanashanmugam,[3] Beatriz Grinsztejn,[19] Sonia Hernandez-Diaz,[13] Patrick Jean-Philippe,[4] Peter Kim,[3] Anne D. Lyerly,[12] Mark Mirochnick,[15] Lynne M. Mofenson,[5] Grace Montepiedra,[14] Jeanna Piper,[3] Leyla Sahin,[7] Radojka Savic,[16] Betsy Smith,[3] Hans Spiegel,[4] Soumya Swaminathan,[20] D. Heather Watts,[17] and Amina White[6]

Table 4. Summary of Consensus Statements

Pregnant and postpartum women should be eligible for all phase III trials designed for treatment of MDR tuberculosis unless there is a compelling reason for exclusion; aminoglycoside drugs, for example, should be excluded during pregnancy because of their teratogenic potential, but this should not preclude evaluation of other promising new agents.
Drug companies developing new tuberculosis drugs should be encouraged to complete reproductive toxicity studies early in drug development, before beginning phase III trials; these data are needed to adequately inform decisions about the inclusion of pregnant women in subsequent clinical trials.
Specific trials of shortened treatment regimens for LTBI should be designed for pregnant women to facilitate treatment completion of regimens and reduce the risk of progression to tuberculosis disease during the high-risk pregnancy/postpartum period.
Targeted PK studies in pregnant and postpartum women should be nested into all trials to provide data on appropriate dosing of drugs during pregnancy and postpartum, when evidence-based dosing guidelines are not already available and particularly when pregnancy is likely to have a significant impact on drug disposition.
A registry should be established to accumulate data on the outcomes of pregnancies exposed to any tuberculosis drugs to allow monitoring of adverse events and to provide data to inform inclusion of pregnant women in clinical trials.

Abbreviations: LTBI, latent tuberculosis infection; MDR, multi-drug resistant; PK, pharmacokinetic.

The More Things Change, the More They Stay the Same?

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i12.557

World J Hepatol 2016 April 28; 8(12): 557-565
ISSN 1948-5182 (online)

MINIREVIEWS

Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women?

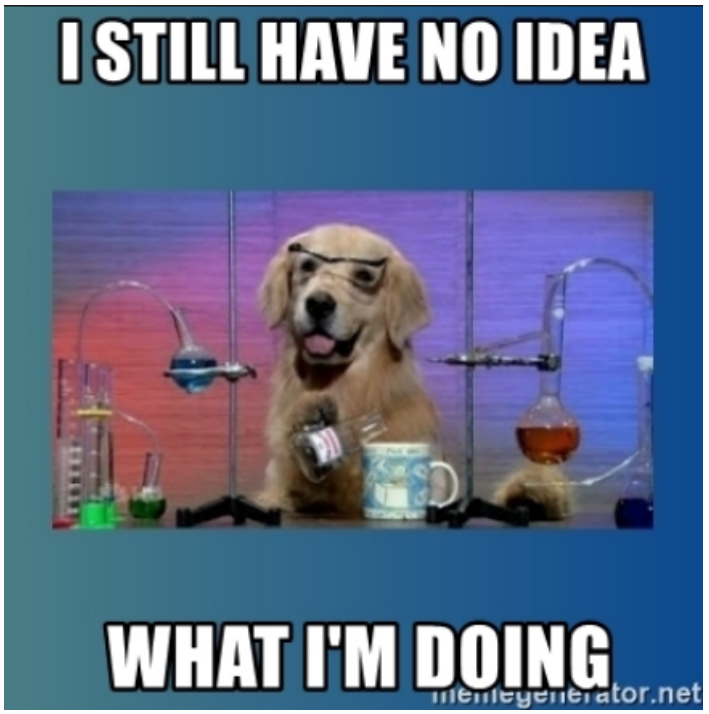
> Currently, all new therapy regimens are contraindicated in this setting because of lack of sufficient safety information and adequate measures of contraception are still routinely recommended for female patients of childbearing potential.

Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

→ Lessons learned: As new drugs are developed for treatment & prevention of HIV/TB (and other significant diseases occurring in pregnancy), studies in pregnant & breastfeeding women are critical and need to be conducted early for promising drugs.

- Update:



Thank You For Your Attention!