

HIV Infection among our youngest: knowledge, survival, resiliency, and opportunity

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Associate Professor of Pediatric and Adult Infectious Diseases Johns Hopkins Medical Institutions NICHD Council Meeting September 13, 2018



Disclosures

- Gilead scientific advisory board
- Merck HIV Global Therapeutic Expert Forum



Global summary of the AIDS epidemic \square 2016

Number of people living with HIV

Total36.7 million [30.8 million-42.9 million]Adults34.5 million [28.8 million-40.2 million]Women17.8 million [15.4 million-20.3 million]Children (<15 years)</td>2.1 million [1.7 million-2.6 million]

People newly
infected
with HIV in 2016Total 1.8 million [1.6 million-2.1 million]
Adults 1.7 million [1.4 million-1.9 million]
Children (<15 years) 160 000 [100 000-220 000]</th>

AIDS deaths in 2016

 Total
 1.0 million [830 000–1.2 million]

 Adults
 890 000 [740 000–1.1 million]

 Children (<15 years)</td>
 120 000 [79 000–160 000]

The Beginning: New York Times (July 1981)



"Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often **rapidly fatal form of cancer.**

The cause of the outbreak is unknown, and there is as yet no evidence of contagion..

.....no apparent danger to nonhomosexuals from contagion..... no cases reported to date outside the homosexual community or in women.

Nine of the victims tested had severe defects in their immunological systems......"



Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.







The First Pediatric Cases

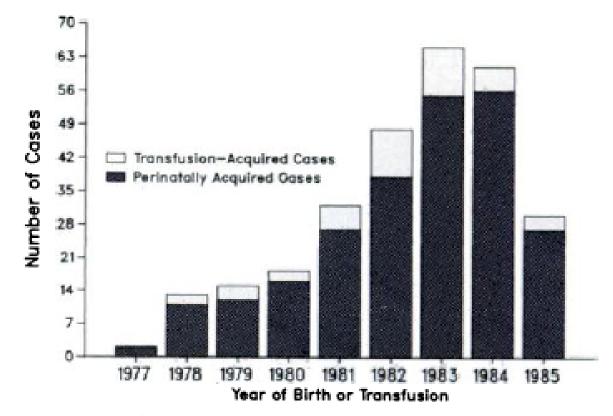


Fig 3. Pediatrics AIDS cases by year of transmission of human immunodeficiency virus. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985. Year of transmission was considered year of birth for perinatally acquired cases and year of transfusion for transfusion-acquired cases.

The First Pediatric Cases



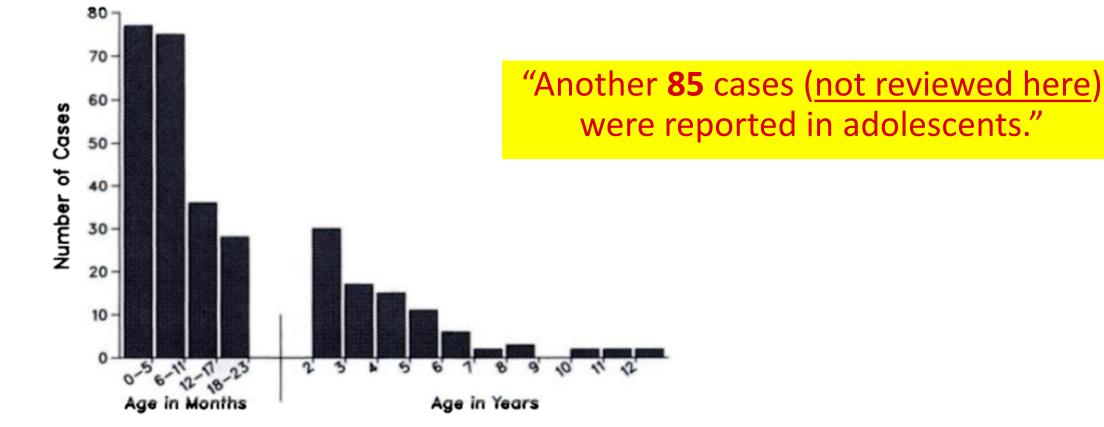


Fig 5. Pediatric AIDS cases by child's age at diagnosis. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985.

Prognosis of perinatal HIV infection

Symptoms develop over months to years
 25% rapidly progress to AIDS (<1 year = highest risk)
 75% experience slow progression
 25% mortality by age five
 Annual rate of disease progression (6-8%)

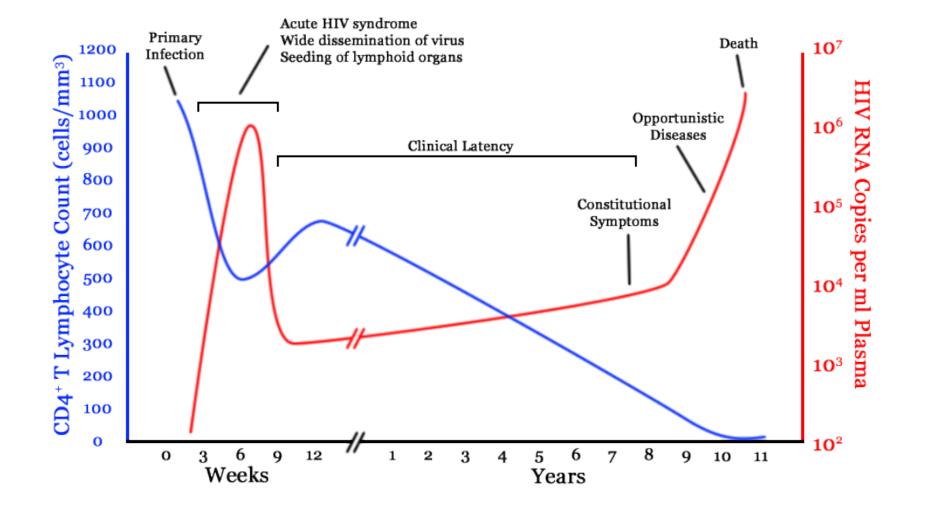


"although they make up only 1% of AIDS patients, they have unique clinical, social, and public health problems that require special attention." Rogers

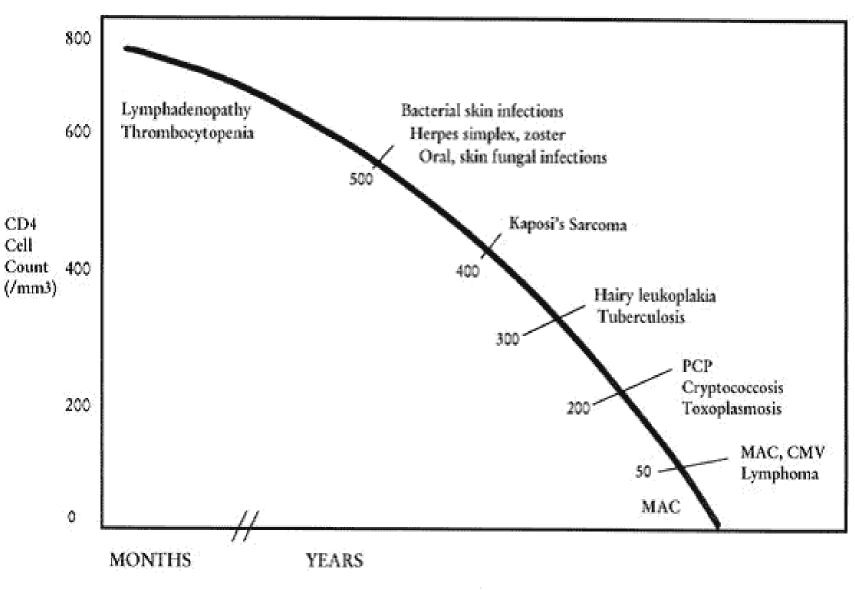




Course of Untreated HIV



CD4 level and Risk of Opportunistic Infections (OIs)



Goals of Therapy

 ↓ HIV-associated morbidity, prolong duration and quality of survival

2)Preserve/restore immunologic function

3)Maximal and durable suppression of HIV viral load

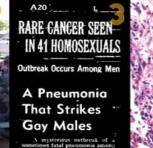
4)Prevent transmission

- Treatment as prevention (TasP)
- Undetectable= Untransmittable (U=U)













~1900s-1960s 🔨 🏊 1975 📣 1978 🗸 1980 — 1981 –

AIDS.

In the early 1900s, transmission of SIV to humans in west-central Africa results in virus mutation and the emergence of HIV-1.

The oldest HIV-1 genomes were sequenced in the 1990s from the preserved tissue samples of a man and woman from the Democratic Republic of Congo who died in 1959 and 1960.

In 1964, Jerome Horwitz synthesizes azidothymidine (AZT) at the Barbara Ann Karmanos Cancer Institute in Detroit. AZT would later be used for the treatment of HIV infection.

Reports of severe wasting syndrome - weight loss of at least 10% of body weight - in residents of Africa, later determined to be symptoms of

A Portuguese After presenting man, "Senhor with Kaposi's sar-José", becomes coma, Ken Horne the first conbecomes the first firmed case of AIDS case to be HIV-2 infection. recognized by the United States.

The CDC publishes reports describing Kaposi's sarcoma and Pneumocystis pneumonia in gay men in California and New York.

The New York Times publishes an article - "Rare Cancer Seen in 41 Homosexuals" - describing cases of Kaposi's sarcoma affecting 41 gay men in San Francisco and New York City.

The first AIDS clinic is established in San Francisco and the Gay Men's Health Crisis is founded in New York City.

Michael Marmor and his colleagues publish a report in The Lancet correlating risk factors for Kaposi's sarcoma with sexual activity and drug use in homosexual men.

The term AIDS is used for the first time by the CDC and is defined as "a disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known case for diminished resistance to that disease.'

The CDC reports on immunodeficiency in female sexual partners of males with AIDS and identifies the primary routes of HIV transmission.

At the Pasteur Institute in Paris, virologists Luc Montagnier and Françoise Barré-Sinoussi isolate a retrovirus (LAV) that kills T cells from a homosexual AIDS patient.

At the NCI in Maryland, Robert Gallo's group identifies the retrovirus (HTLV-III) to be the cause of AIDS.

U.S. Health and Human Services Secretary Margaret Heckler declares that a vaccine will be available for HIV within two years.

Project SIDA, the first AIDS research project in Africa is launched.

The FDA approves the ELISA blood test kit used to screen for antibodies against HIV in the U.S. blood supply.

The Canadian Red Cross begins screening blood products for HIV.

The first International AIDS conference is held in Atlanta.



1987. **~1986•**

Robert Gallo's HTLV-III and the LAV discovere by Montagnier and Bar Sinoussi are identical and the retrovirus is named HIV.



The FDA approves zidovudine (AZT) – the first antiretroviral drug – for the treatmen of HIV infection.

The FDA approves the first clinical trial of an HIV vaccine candidate

1988

The largest needle exchange program, Prevention Point, is established in San Francisco.

The first World AIDS Day is held on December 1.

UNAIDS (Joint United Nations Programme on HIV/AIDS) reports that more women are living with HIV/AIDS than men in sub-Saharan Africa.



•1990<u>s-2014</u> •••

In 1995, the FDA approves the first protease inhibitor drug, saquinavir, which makes highly active antiretroviral therapy (HAART) possible.

In 2007, Timothy Kay brown is cured of HIV following a bone marrow transplant to treat his leukemia.

In 2012, approximately 35.3 million people are living with HIV/AIDS worldwide. In Sub-Saharan Africa, 1 in 20 adults are living with HIV.

In 2014, the U.S. federal funding for HIV/AIDS research is USD \$29.7 billion.

PHOTO CAPTIONS

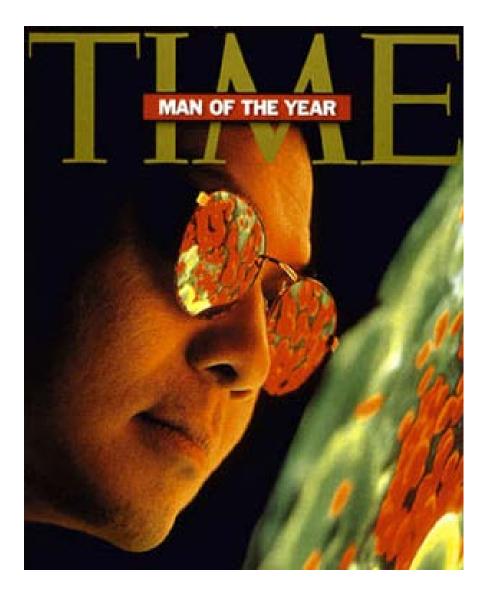
1. ORIGINS - Chimpanzee (flickr: Tim Ellis) 2. EFFECTS - Children orphaned by HIV/AIDS, Malawi (flickr: khyme54) HEADLINES - New York Times (Top), San Franscisco Chronicle (Bottom) 1981 4. INFECTION - Kaposi's Sarcoma, H&E stain (flickr: Yale Rosen) 5. DISCOVERY - Françoise Barré-Sinoussi, Luc Montagnier (flickr: PhOtOnQuAnTiQuE) 6. AWARENESS - HIV signpost, Cameroon (flickr: Joel Abroad) 7. DIAGNOSIS - ELISA blood test for HIV antibodies (flickr: LSC) 8. BIOLOGY - HIV infected T cell (flickr: NIAID) 9. TREATMENT - AZT photomicrographs (flickr: Kat Masback) 10. SUPPORT - AIDS Walk 1988, Los Angeles (flickr: Mr Flikker) 11. PROTEST - ACT UP protest 1988, FDA headquarters (flickr: The U.S. FDA) 12. SOLIDARITY - World AIDS Day 2013, White House North Portico (flickr: Ted Eytan) 13. EDUCATION - Teaching children, Central African Republic (Pierre Holtz, UNICEF)

14. STATUS - HIV blood tests for children of HIV+ mothers, Tanzania (flickr: kim)

Designed and written by Ben X. Wang



Advances in management of HIV



Diagnostic tools

- Opportunistic infection prophylaxis and treatment
 immunizations
- Antiretroviral treatment
- Identification, management, and prevention of co-morbidities

Unique clinical issues for children

Prevention of mother to child acquisition
 Antiretroviral treatment for children

 dosing, formulation, palatability, toxicity

 Prophylaxis of opportunistic infections
 Identification of co-morbidities
 Treatment of co-morbidities
 Immunizations



and the second s



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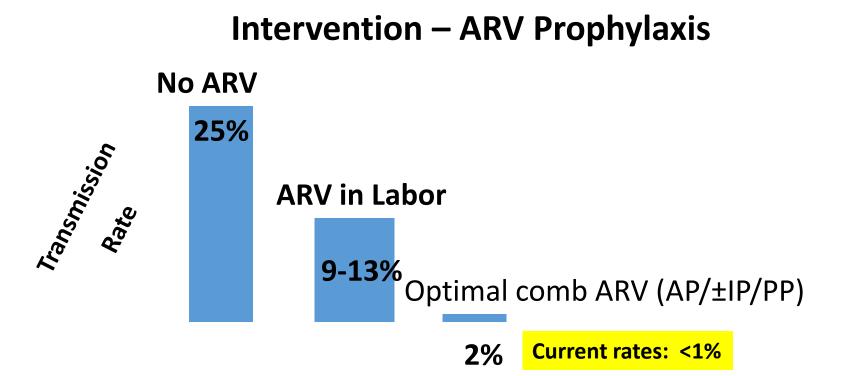
Number 18

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*



Risk of Perinatal Transmission Decreased



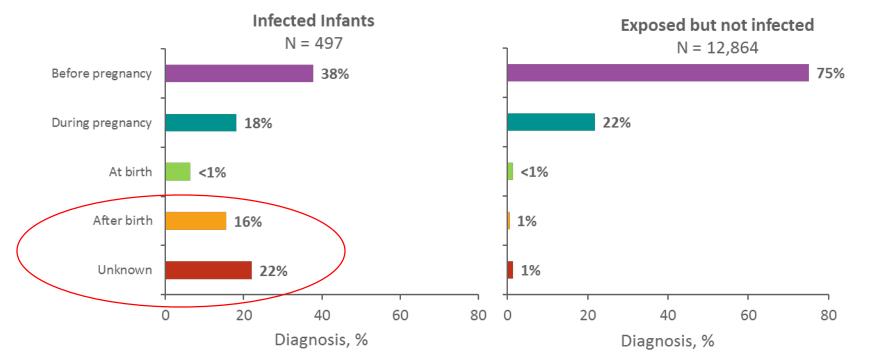
Wade, et al. 1998 NEJM 339;1409-14 Guay, et al. 1999 Lancet 354;795-802 Fiscus, et al. 2002 Ped Inf Dis J 21;664-668 Moodley, et al. 2003 JID 167;725-735 Nielsen-Saines, et al NEJM 21;366(25):2368-79 Fowler, Mofenson, Taha. N Engl J Med. 2017







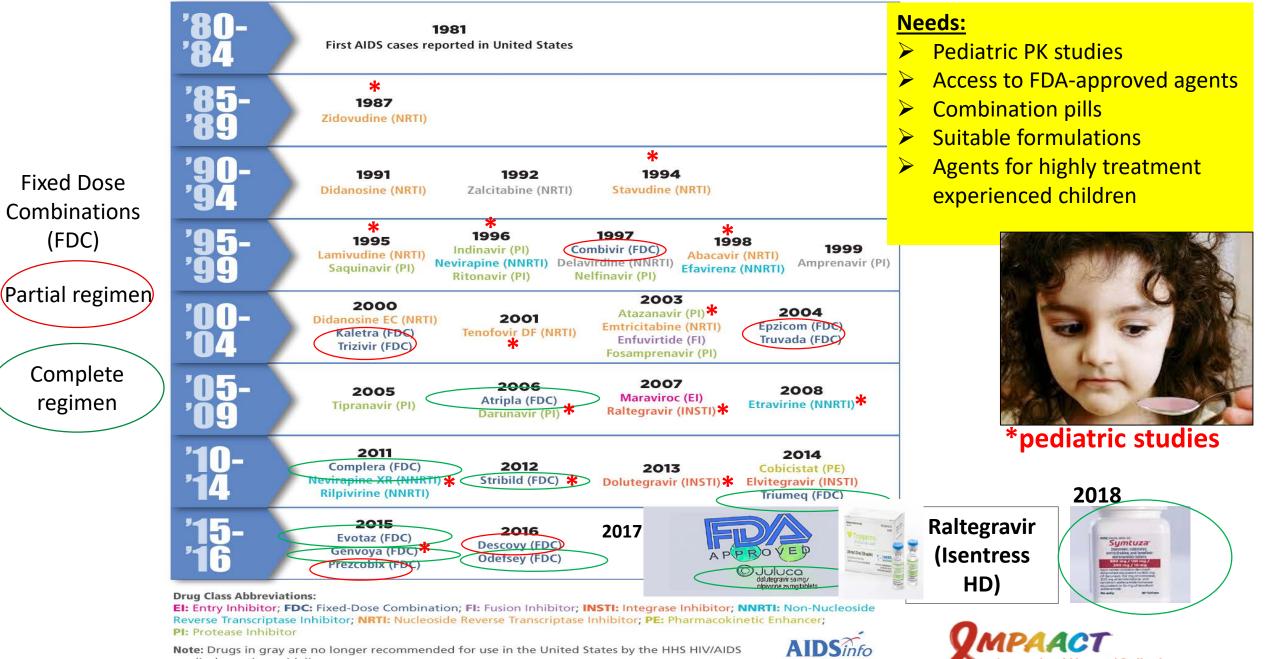
Time of Maternal HIV Testing among Children with Diagnosed Perinatally Acquired HIV Infection and Children Exposed to HIV, Birth Years 2009–2013—United States and Puerto Rico



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.



FDA Approval of HIV Medicines



medical practice guidelines.

International Maternal Pediatric Adolescent AIDS Clinical Trials Network



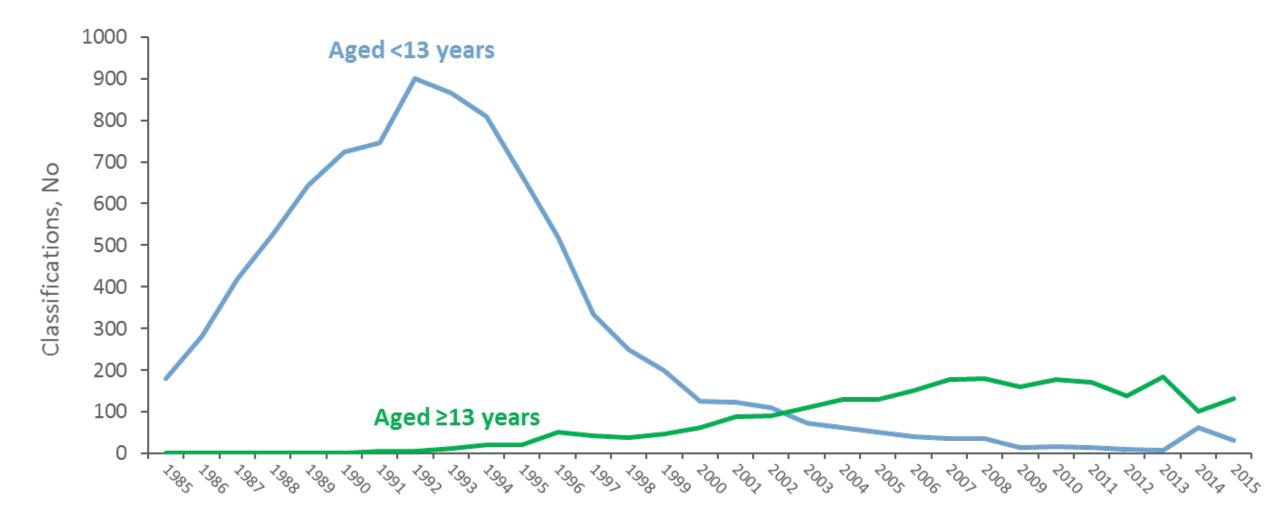
Prevention of illness

- >Optimization of OI prophylaxis
- ➢Improve ab responses to vaccination
 - ≻HPV
 - ≻HBV
 - ➤Meningococcus
 - ≻Influenza
 - ➢ Rotavirus
 - ≻RSV

Vaccine	Age											
	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	24 mos	4-6 yrs	11-12 yrs	14-16 yrs
Recommendations for these vaccines are the same as those for immunocompetent children												
Hepatitis B [†]		Hep B1									Han	
		Hep B2			Hep B3					(Hep B)		
DTaP [§]			DTaP	DTaP	DTaP		TD	aP		DTaP	т	ď
Haemophilus influenzae type b [¶]			Hib	Hib	Hib	Н	ib					
Inactivated polio**			IPV	IPV		IP	v			IPV		
Hepatitis A ^{††}											Hep A ir ected ar	
Recommendations for these vaccines differ from those for immunocompetent children												
Pneumococcus ^{§§}			PCV	PCV	PCV	PC	cv		PPV23	PPV23 (age 5-3 yrs)		
MMB ^{¶¶}						M	ИR			MMR	MMR	
		Do n	ot admi	nister to	severe	ly immu	nosupp	ressed	Categor	y 3) chi	ldren	
Varicella ^{***}						Var	Var				Var	
vancena	Administer only to asymptomatic nonimmunosuppressed (Category 1) children; contraindicated for all other HIV-infected children											
Influenza (inactived) ⁺⁺⁺	A dose is recommended every year											
(inactived)	Live influenza vaccine should not be given to HIV-infected patients											
Range of recommended ages for vaccination Recommended in selected states or regions												
Vaccines to be administered if previously recommended doeses were missed or were administered at other than the recommended minimum age												

HIV Web Study (www.HIVwebstudy.org)

Stage 3 (AIDS) Classifications among Persons with Perinatally Acquired HIV Infection, 1985–2015—United States and 6 Dependent Areas





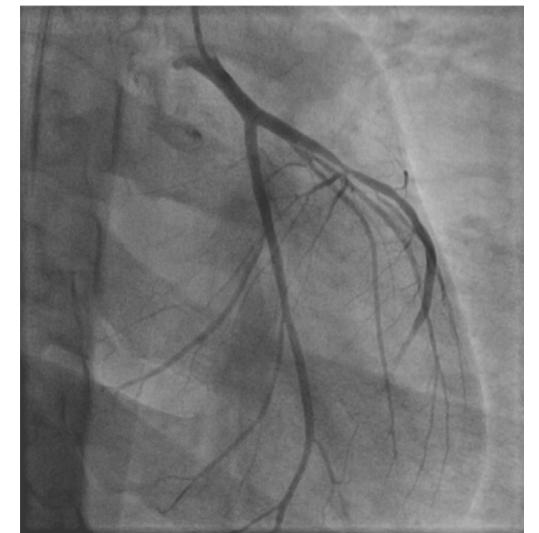
Year of classification



Long-term Morbidity of HIV and/or ART

- Cardiovascular disease
- ➤ Malignancy
- Medication side effects:
 - ➢ Kidney, bone, liver
- Metabolic abnormalities:
 - mitochondrial toxicity
 - lipodystrophy
 - lipoatrophy
- Longstanding inflammation
- CNS abnormalities
 - strokes, cognitive effects, mental health
- ≻ Unknown?
 - Consequences of lifelong ART?
 - Consequences of lifelong HIV?

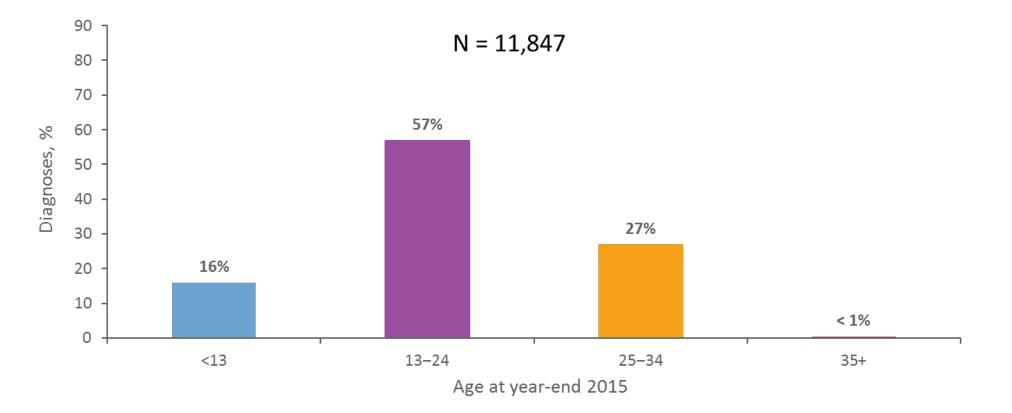




Hazra R et al.; Griffith D et al OFID 2017, Izbudak AJNR 2013, Venkataramani M AIDS Pt Care STDs 2010.



Age Distribution of Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2015—United States and 6 Dependent Areas

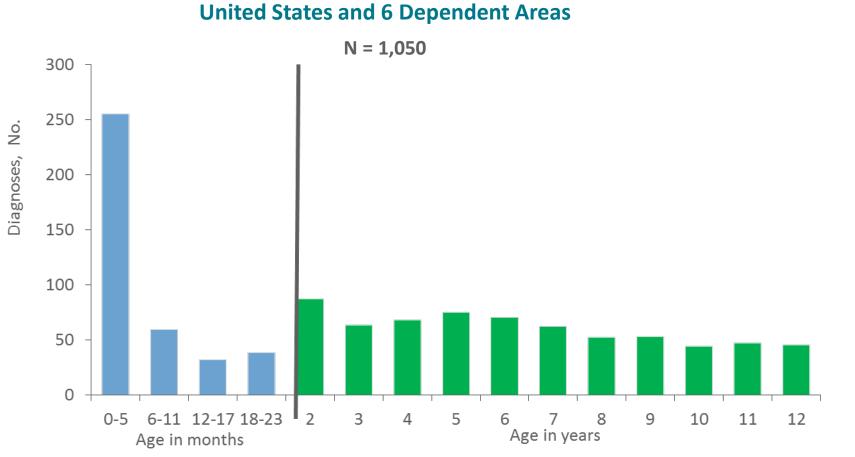






*

Diagnoses of HIV Infection among Children Aged <13 Years, by Age at Diagnosis, 2010–2014—



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.



The First Pediatric Cases



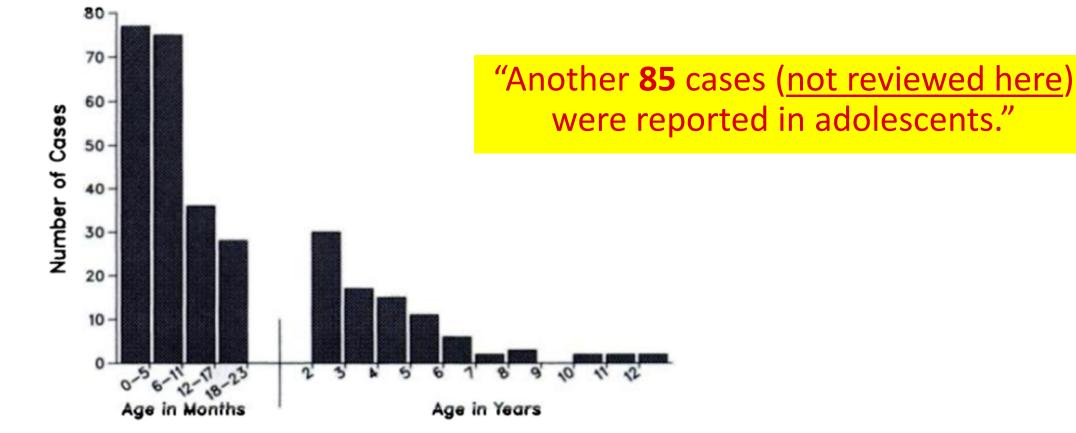
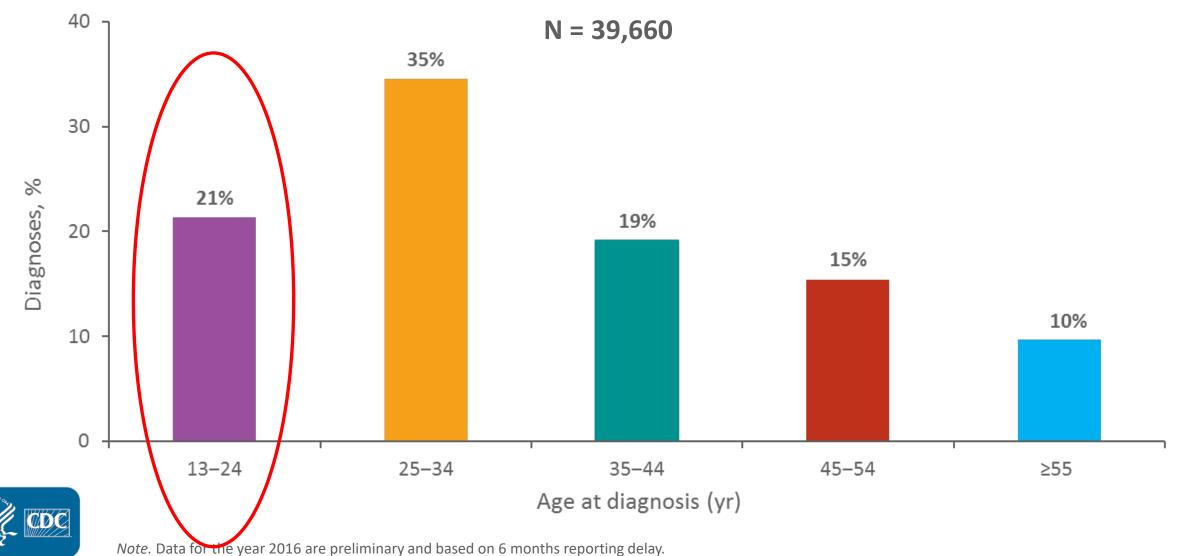


Fig 5. Pediatric AIDS cases by child's age at diagnosis. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985.

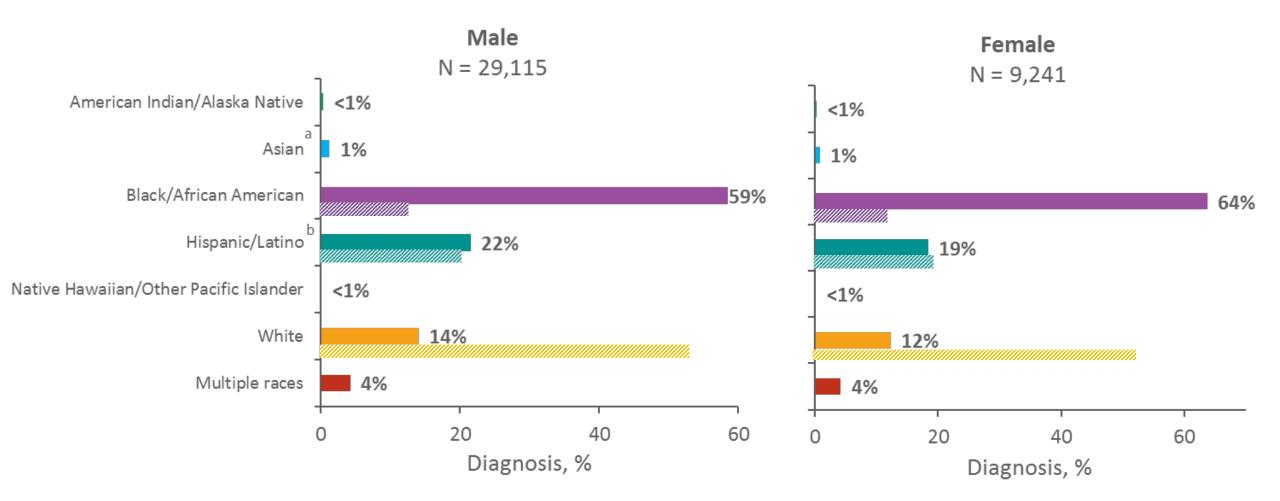


Diagnoses of HIV Infection among Adults and Adolescents

by Age at Diagnosis, 2016—United States



Adolescents and Young Adults Aged 13–24 Years Living with Diagnosed HIV Infection, by Sex and Race/Ethnicity, Year-end 2014—United States and 6 Dependent Areas

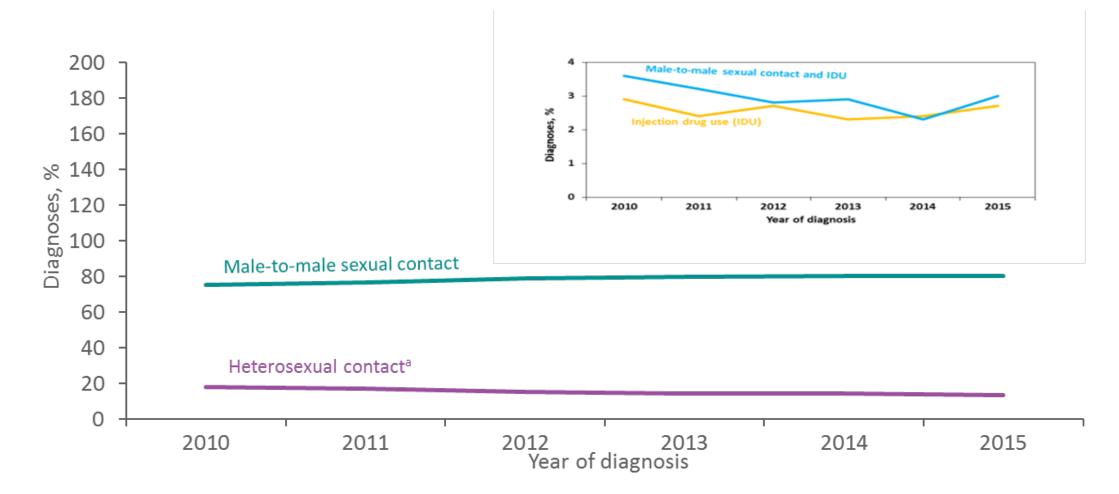




Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.

- ^a Includes Asian/Pacific Islander legacy cases.
- ^b Hispanics/Latinos can be of any race.

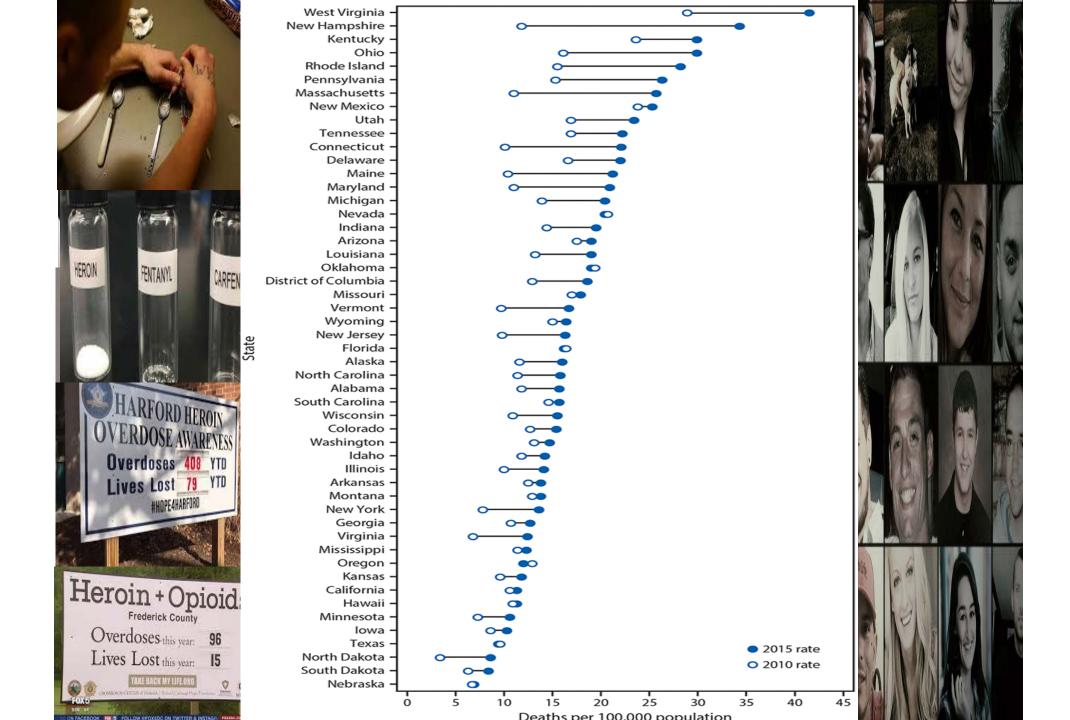
Diagnoses of HIV Infection among Adolescents and Young Adults Aged 13–24 Years, by Transmission Category, 2010–2015—United States and 6 Dependent Areas





Note. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises less than 1% of cases.

^a Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.



Prevention...

Will using PrEP cause

problems

with the hormones I

am taking??

PrEP

NATE

HO

YOU

When transgender women

How much would PrEF

cost?

Would they

even prescribe PrEP for a

woman like me?

choose to take PrEP

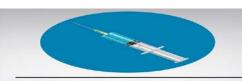
How much do they know about how our about how our transgender transgender transgender transgender transgender

#PrEPForHer

D



PrEP



70% Daily PrEP can reduce the risk of HIV infection among people who inject drugs by more than 70%.

UVL



#LetsTalkAboutPrEP

Prep + HIV TREATMENT + CONDOMS

CONDOMS

PrEP is a safe, daily pill that helps prevent HIV. PrEP Find yours at PrEPForHer.com







Medical challenges

	Perinatal	Non-perinatal
Disease		
Advanced disease/immunosuppression	Х	*
Co-morbidities [⊥]	Х	*
Neurocognitive delay and dysfunction	Х	*
Mental health (anxiety, depression, PTSD), substance use	Х	Х
Delayed puberty and short stature	Х	
Suboptimal responses to vaccines	Х	*
Treatment		
Treatment experienced	Х	*
More complicated ART	Х	*
Treatment fatigue	Х	Х
Drug-resistant virus	Х	*



*some NPHIV youth

Psychosocial challenges

	Perinatal	Non-perinatal
Stigma (HIV, sexuality)	Х	Х
Disclosure (HIV, sexuality)	Х	Х
Limited support systems	Х	Х
Clinical staff may be only reliable support	Х	Х
Poor adjustment to illness/status, self efficacy, outcome expectancy	Х	Х
Denial/guilt	Х	Х
Limited health literacy	Х	Х
Logistic barriers: insurance, childcare, transportation, poverty, legal	Х	Х
Attempting to be "normal"	Х	Х





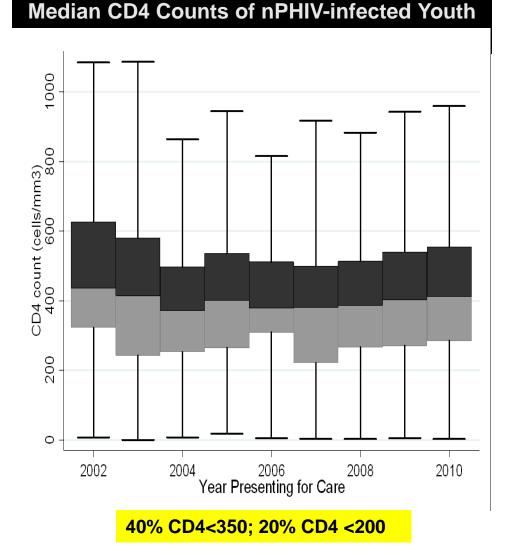


Murphy JAMA 2003; Martinez Pediatrics 2014; Mofenson JIAS 2015; Rudy AIDS Pt Care 2009 & 2010; Lee & Hazra JIAS 2015

Clinical Observations \rightarrow Research Questions



- > Youth presenting with advanced HIV
- Youth less likely to initiate ART
 - CD4 recovery not better
- Providers reluctant to start ART
- > Youth have worse outcomes
 - poor virologic suppression
 - ➤ continuing failing ART
 - ART discontinuation
 - high hospitalizations
 - Poor retention in care
- Youth do better in pediatric & adolescent vs. adult settings
 - Differences in how providers of varied training interact with youth

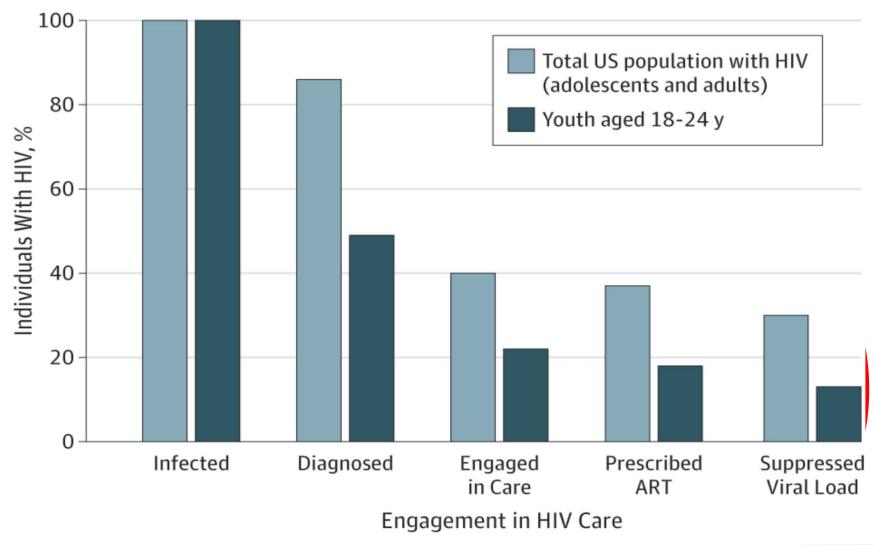


Agwu et al. JAMA Peds 2014, JAH 2012 & 2014 (Lee), JAIDS 2011 & 2014, JPIDS 2013 (Farmer) & 2014 (Berry), PIDJ 2014, AIDS Pt Care 2008; PLOS One 2017; Ryscavage PA et al. JAIDS 2011

Agwu KL2, NIAID K23



Continuum of care for YHIV



"What are we missing?"

≻Life is dynamic

Adherence is hard & multifactorial

➢Side effects

Long term toxicity

➢One size does not fit all

➢ Forever is a long time

➢ Fatigue

➢ Disclosure

≻Stigma

≻Mental health

"I don't want to be here?"





Simplifying treatment: better drugs

➤Fewer pills

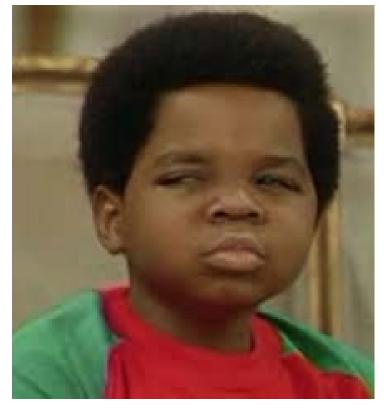
- Combination pills
- One-pill regimen options
- Once daily options
- ➤Smaller pill size
- ➤More formulations
- More delivery options
- ➢ Better taste
- ➤ Higher barrier to resistance
- Fewer drug-drug interactions
- ➤Fewer side effects
- Fewer dietary requirements
- More options for treatment-experienced individuals





Simplifying treatment: fewer agents?

- ≻2 drug regimens
- ➢NRTI-sparing regimens
- Decreased drug interactions
 - Dolutegravir/rilpivirine (Juluca)
 - Non-inferior to 3-drug regimen
 - Dolutegravir/lamivudine
 - > Adults: switch to 3TC/DTG \rightarrow no VF, improved CD4, reduced cost
 - Pediatrics??





Simplifying treatment: are pills even needed?



Population: 309 treatment-naïve, HIV+

92% male; 15% AA, 79% White, median age 35, baseline CD4 489 Location: USA, Canada, Spain, France, and Germany Meds: oral cabotegravir , rilpivirine, and abacavir Intramuscular cabotegravir and rilpivirine (two 2 mL injections)- buttocks Method:

All start oral \rightarrow suppress

→ continue oral cabotegravir/rilpivirine/abacavir

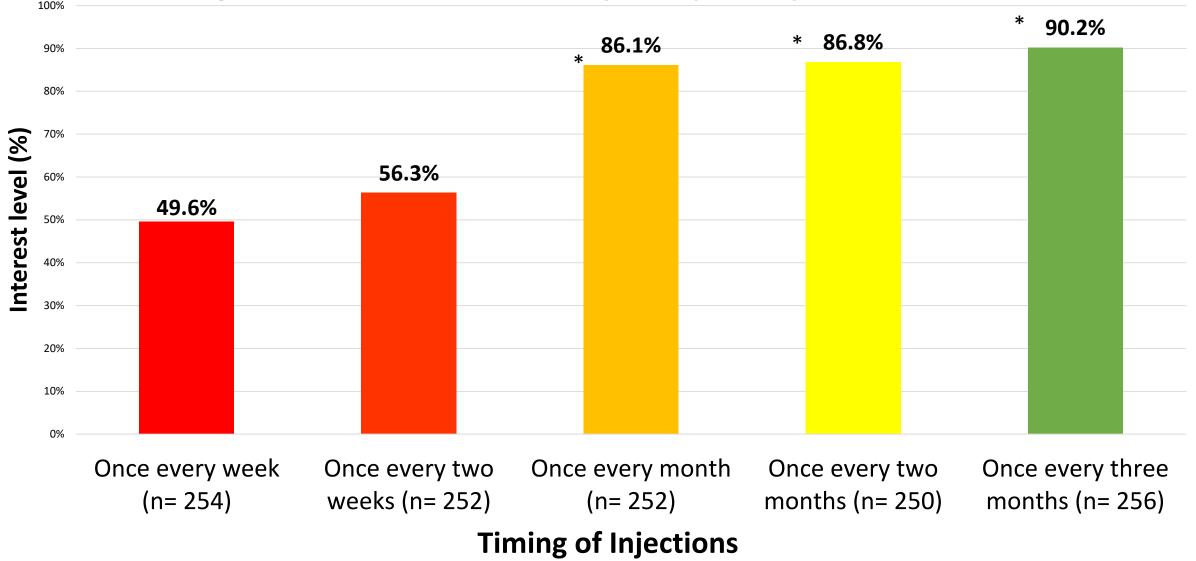
 \rightarrow IM cabotegravir/rilpivirine every 4 weeks

 \rightarrow IM cabotegravir/rilpiviriine every 8 weeks

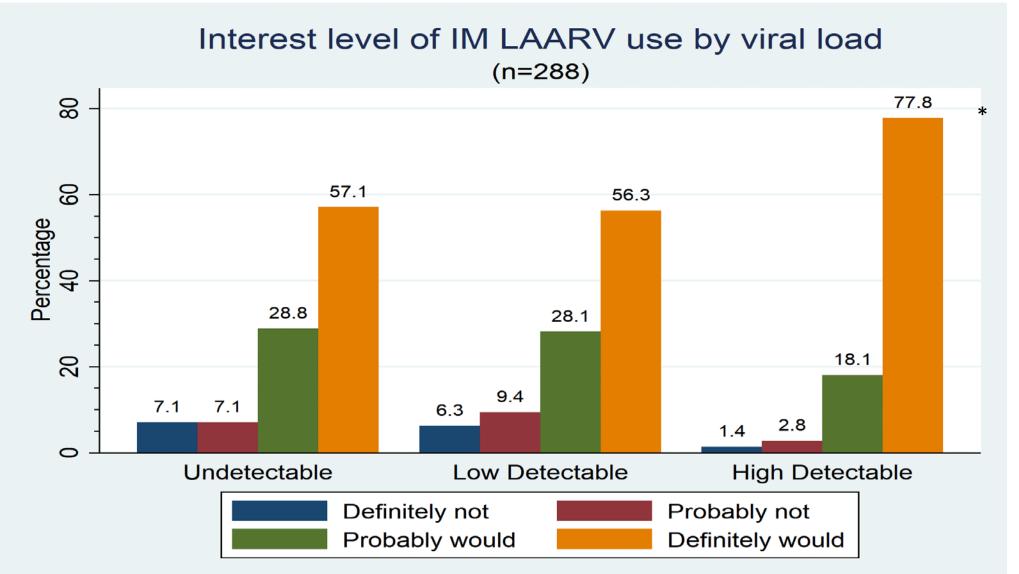




Youth willingness to use LA-ART by frequency of administration



Impact of non-adherence on interest among youth



*p<0.05; significance tested by adjusted Poisson regression, robust variance

Weld et al. IAS 2017



Development Pipeline for Long-Acting ART

Cabotegravir & rilpivirine LA --Phase IIb

≻FLAIR

►ATLAS

≻HPTN 083

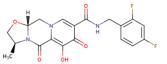
≻HPTN 084

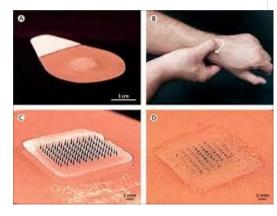
➤ACTG 5359

►IMPAACT 2017

►IMPAACT 2022*

≻MK-8591 (EFdA)

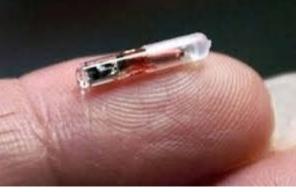






An injectable combination therapy could replace oral medications and experts think it may improve adherence rates.





*in development

[hivplusmag.com/treatment/2015/11/09/monthly-shot-could-soon-replace-daily-hiv-meds]



Beyond ART

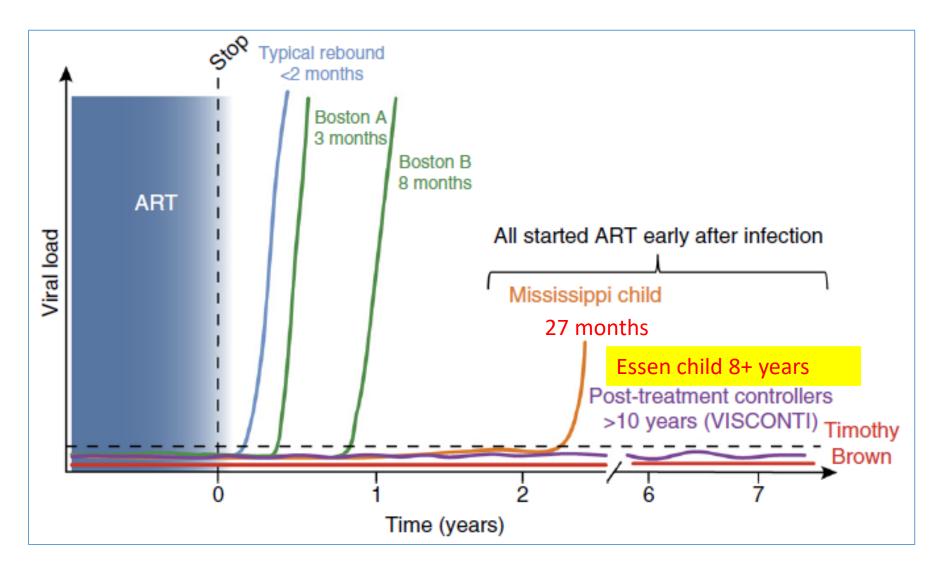




"Forever is a long time" Beyond viral suppression as a destination....



Outcome Measure to Detect HIV-1 Remission: Time to Viral Rebound





IMPAACT P1115

VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

A Multi-Center Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

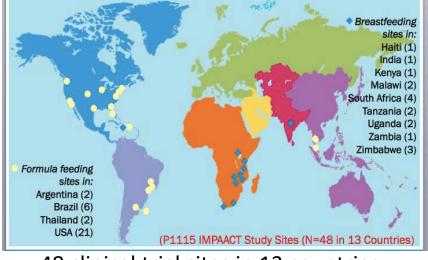
Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID) and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by: Merck Research Laboratories National Institute of Allergy and Infectious Diseases Vaccine Research Center

DAIDS ES #11954 IND # TBA

IMPAACT CURE Scientific Committee Chair:	Deborah Persaud, M.D.
Protocol Co-Chairs:	Yvonne Bryson, M.D. Ellen Chadwick, M.D.
Protocol Vice Chair:	Mark Cotton, M.Med. FCPaed
NIAID Medical Officer:	Patrick Jean-Philippe, M.D.
NICHD Medical Officer:	Rohan Hazra, M.D.
Clinical Trials Specialists:	Anne Coletti, M.S. Charlotte <u>Perlowski</u> , M.S.P.H.



48 clinical trial sites in 13 countries

October 2017:

Version 1:

Step 1:Enrolled 440 mother-infant pairsStep 2: 34 infected infants (Cohort 1)Step 2: 18 infected infants (Cohort 1)Step 3: ART cessation to detect remissionStep 4: Restart ART for viremic rebound

December 2017: Version 2 additional 445 mother-infant pairs (ARVs +/- bNAbs)





Where should the Science be moving?

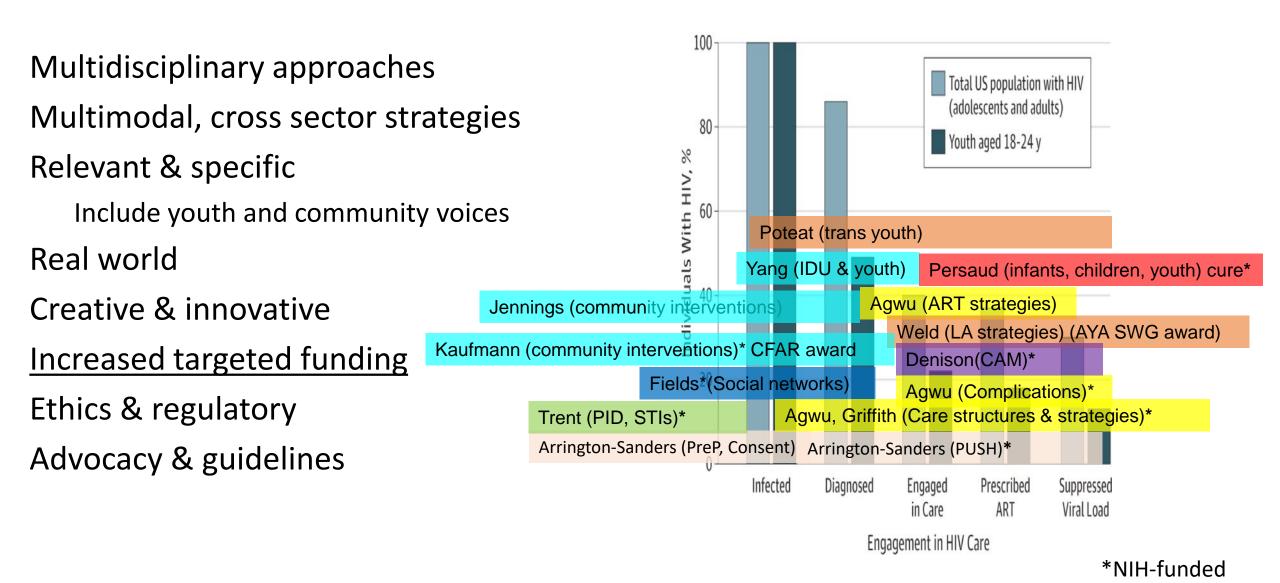
> Multimodal strategies & approaches for treatment, prevention, remission

- Biologics (e.g., monoclonal ab, activated T cells)
- > Other agents (e.g., latency reversing agents)
- > ART next gen (e.g., long-acting, different delivery modes)
- Predicting and addressing complications
 - Longitudinal cohorts, biomarkers, surrogates
- Behavioral and community interventions
 - Improved finding & targeting strategies
- Implementation science
- Optimizing care models
 - ➢ Rapid initiation
 - Alternative "venues" for care delivery
 - ≻ Tech
- Personalized medicine?
 - > Proteonomics, Metabolomics, microbiome





Focusing on youth: JHU Projects and Initiatives





Acknowledgements

The Youth!!

ACE team

IPC/PAHAP

Bartlett Clinic (Keruly, Moore, Nolan)

JHU HIV Clinical Research team (IMPAACT, ATN, Cure)

Trent, Persaud, Arrington-Sanders, Anderson, Collensen-Streng Farmer, Griffith, Lee, Hsu, Weld



Gebo, Moore, Fleishman, Yehia, Berry, Gaur, Korthuis, Rutstein, Voss, Monroe, co-investigators, sites, and participants





Health Resources and Services Administration

Maternal and Child Health Bur

