

Overview of cohorts of HIV-infected women and girls



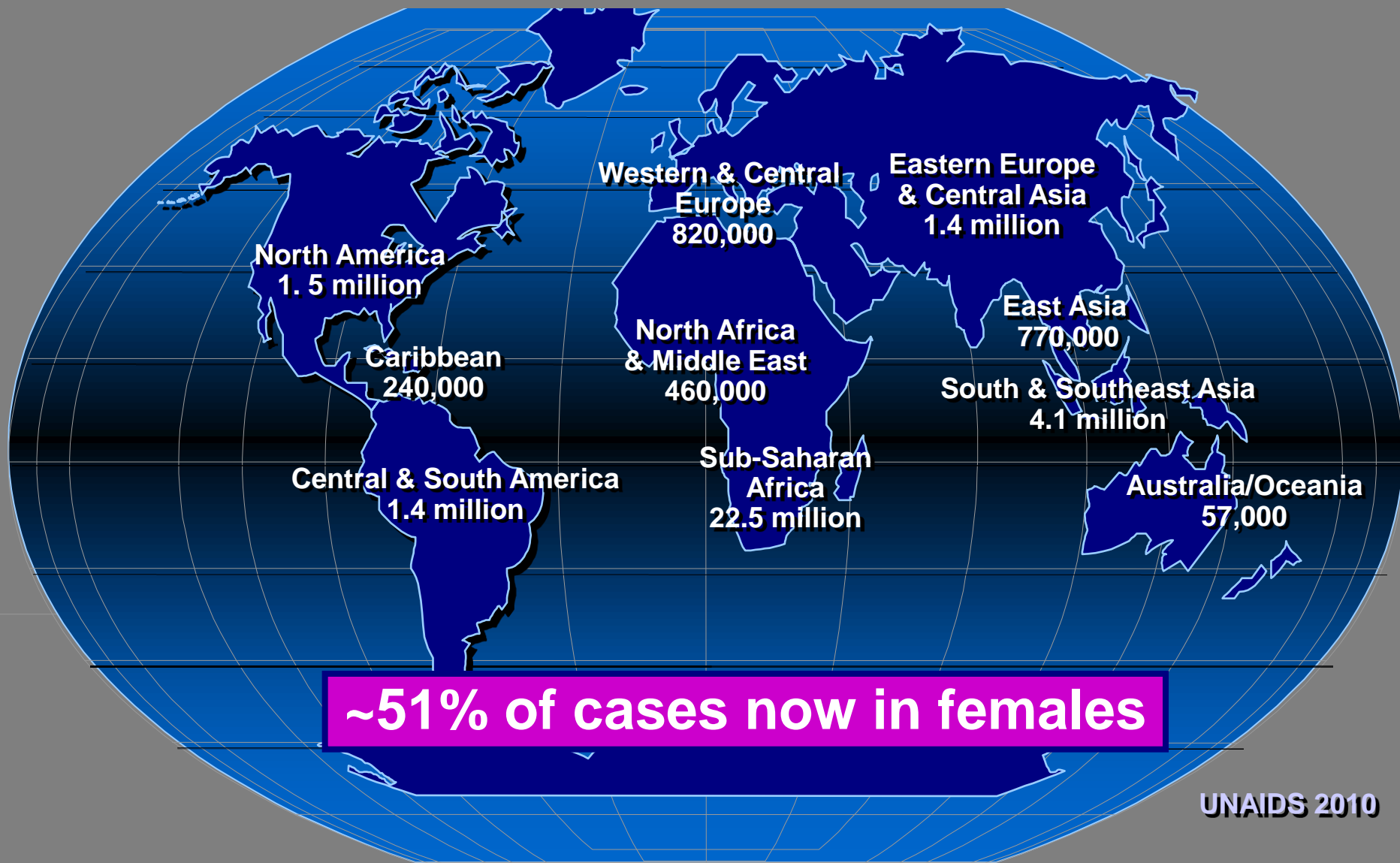
WRI March 17-20, 2011

Monica Gandhi MD, MPH

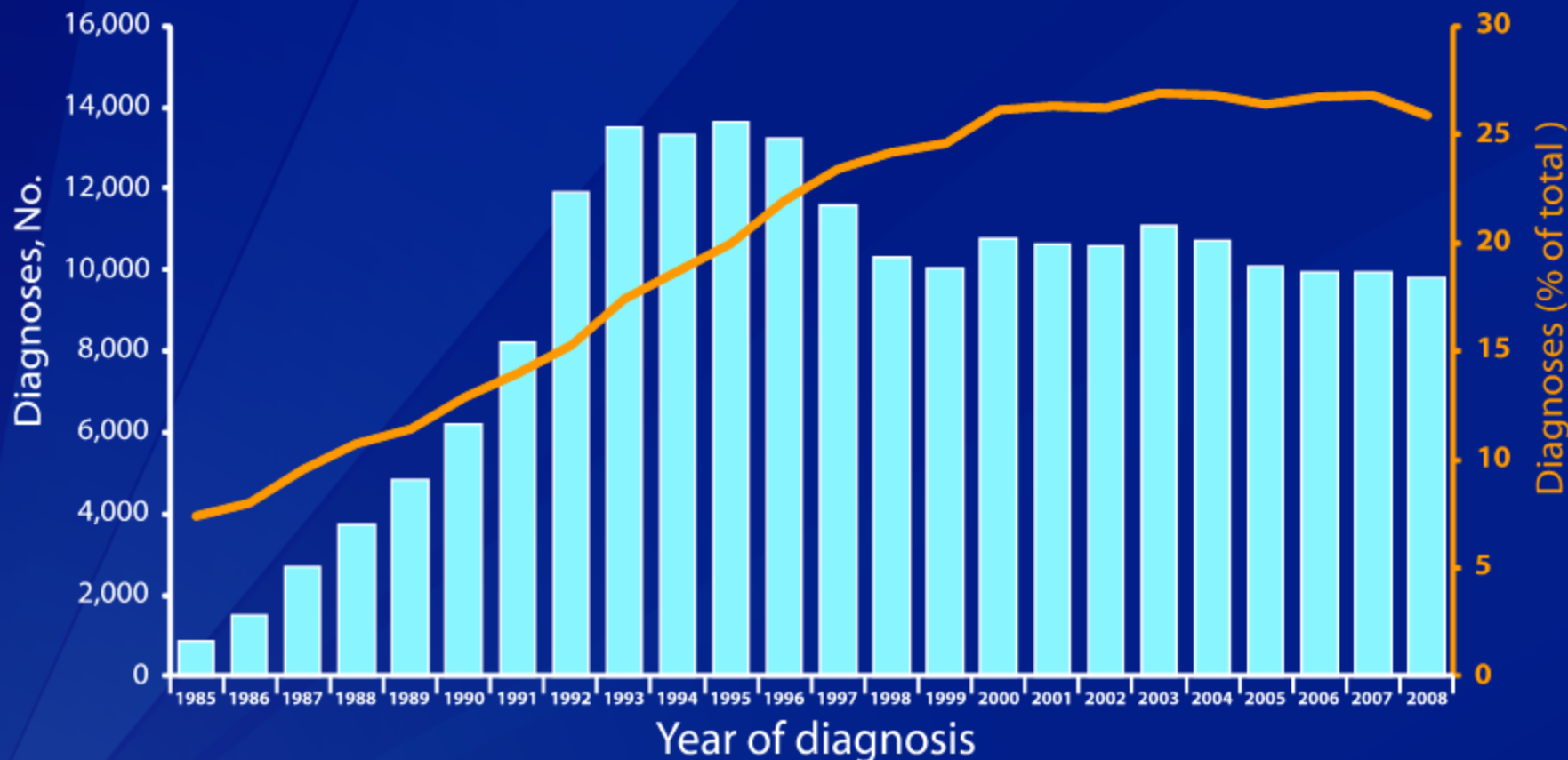
**Associate Professor, Divisions of HIV/AIDS and Infectious Diseases
Director, HIV Consult Service, University of California, San Francisco (UCSF)**

HIV pandemic (adults & children) by end-2009

TOTAL 33.3 (31.4-35.3) million



AIDS Diagnoses among Adult and Adolescent Females, 1985–2008—United States and Dependent Areas



Note. All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.



Diagnosis of HIV infection in Adults and Adolescents by Race/ Ethnicity CDC 2008 (cases/100,000 population)

Race	Female (11.5)	All Male (35.9)
Black/ African-American	56.0	131.9
Hispanic/ Latino	13.3	52.3
White	2.9	16.6
American-Indian / Alaskan Native	6.9	23.4
Asian	3.0	15.8
Native Hawaiian/ Other Pacific Islander	10.6	48.2
Multiple races	11.9	33.6

Diagnoses of HIV Infection among Adult and Adolescent Females, by Transmission Category and Age at Diagnosis, 2008—37 States and 5 U.S. Dependent Areas

Transmission category	Age at Diagnosis (in years)				
	13–19	20–24	25–34	35–44	≥45
	%	%	%	%	%
Injection drug use	9.5	10.4	13.1	15.7	18.9
Heterosexual contact ^a	90.5	89.5	86.7	83.9	79.3
Other ^b	<0.1	0.1	0.2	0.4	1.8
Total	100	100	100	100	100

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data from 37 states and 5 U.S. dependent areas with confidential name-based HIV infection reporting since at least January 2005.

All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays and missing risk-factor information, but not for incomplete reporting.

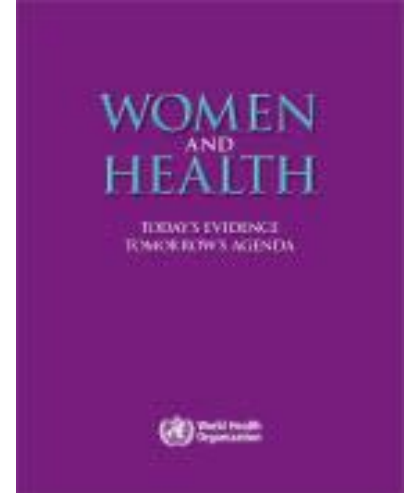
^a Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

^b Includes blood transfusion, perinatal exposure, and risk factor not reported or not identified.





Massive impact in women



- ***Women and health: today's evidence tomorrow's agenda*** released by the World Health Organization (WHO) on November 9, 2009
- **“Globally, the leading cause of death and disease among women of reproductive age (between the ages of 15 and 44) is HIV/AIDS. . . .”**

November 9, 2009;

<http://www.who.int/gender/documents/9789241563857/en/index.html>

Daunting task. . So many cohorts

• NIH-funded cohorts

- International Epidemiologic Databases to Evaluate AIDS (IeDEA)
- Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS)
- Women's Interagency HIV Study (WIHS)
- Pediatric HIV/AIDS Cohort Study (PHACS)
- NICHD International Site Development Initiative (NISDI)
- Women's HIV Interdisciplinary Network (WHIN)
- Multicenter AIDS Cohort Study (MACS)

• NIH-funded clinical trials with cohorts

- Microbicide Trials Network (MTN)
- International Maternal-Pediatric-Adolescent AIDS Clinical Trials (IMPAACT) Group
- Adult AIDS Clinical Trial Group: ALLRT cohort
- Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions
- HIV Prevention Trials Network cohorts

• Everything else

- Europe
- Canada
- Australia
- Latin America
- Africa
- India



- **CDC**
 - HERS
 - SUN

A world map in light blue and yellow tones serves as the background. A prominent red AIDS ribbon is positioned on the right side, overlapping the letters 'E' and 'A' of the main title.

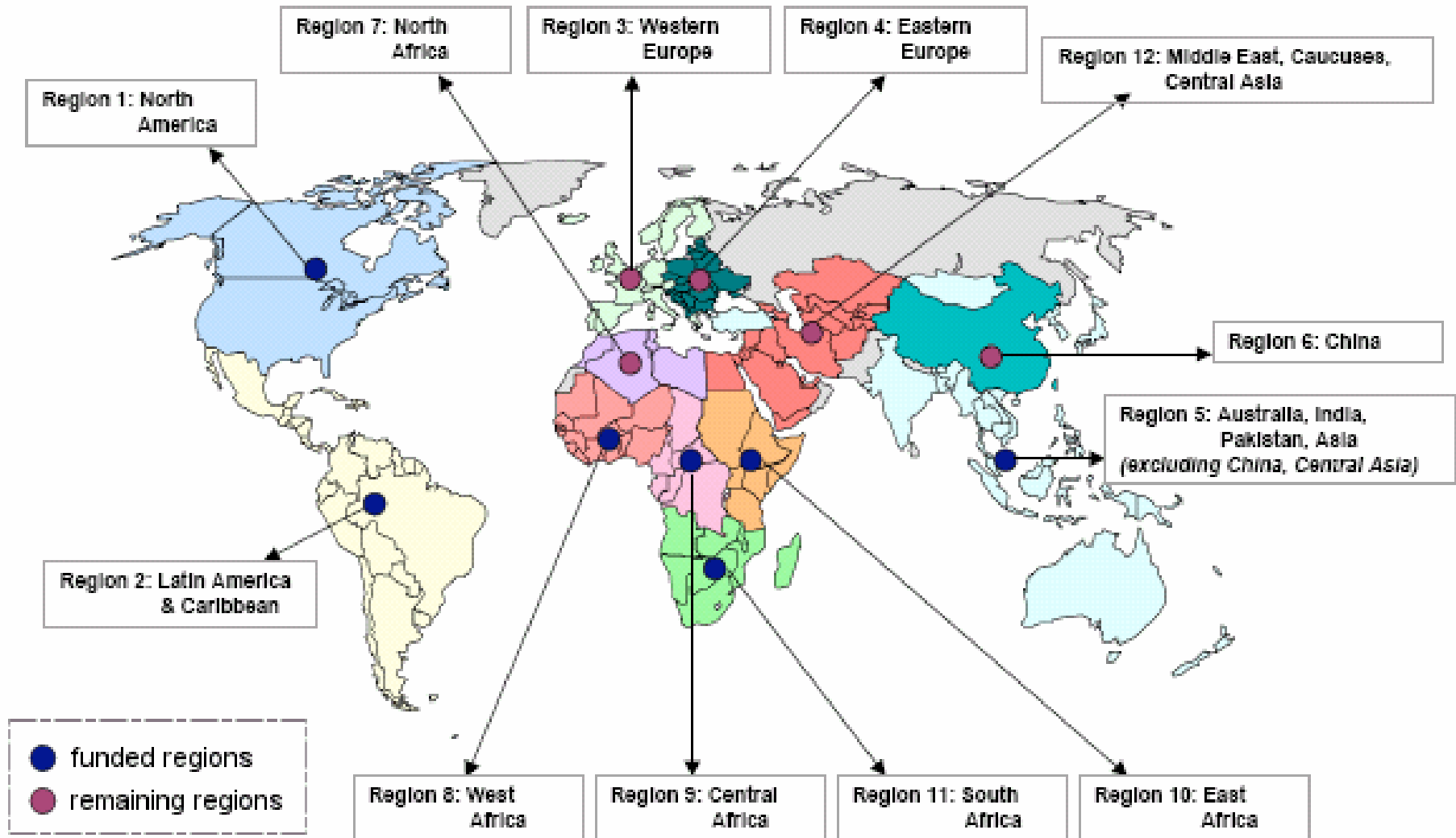
IeDEA

**International epidemiologic
Databases to Evaluate AIDS**







International epidemiology Databases to Evaluate AIDS

- **12 regions defined (7 funded), one data center funded per region**
- **Regional leDEAs**
 - Identify and pursue relevant regional research
 - Adults and children
 - Serve as a resource for region
 - Data collection, standards and harmonization of data
 - Data management, storage, analysis
- **Global coordination between leDEA regions**
 - Pursue “continental questions”
 - Work towards harmonization globally
 - Chair (from PIs) serves for 2 yrs

12 regions defined; 7 funded (active)



Global leDEA Regions

Region	PI	Institution
North America (NA-ACCORD)	Richard Moore 	Johns Hopkins University
Caribbean Central and South America (CCASA-net)	Daniel Masys 	Vanderbilt University
Australia/Asia/China (APHOD/, TApHOD)	David Cooper 	AMFAR
West Africa (WADA)	François Dabis 	Victor Segalen University, Bordeaux France
Central Africa	Ty Hartwell	Research Triangle Institute
East Africa (REACT)	Constantin Yiannoutsos 	Indiana University
South Africa (OASIS)	Matthias Egger 	University of Bern, Switzerland

IeDEA countries (# 43)

Region 1: North America NA ACCORD

- Canada
- United States

Region 5: Australia, India, Pakistan, Asia APHOD

- Australia
- Cambodia
- China
- India
- Indonesia
- Japan
- Malaysia
- Philippines
- Singapore
- South Korea
- Taiwan
- Thailand

Region 2: Latin America & Caribbean CCASAnet

- Argentina
- Brazil
- Chile
- Haiti
- Honduras
- Mexico
- Peru

Region 9: Central Africa

- Burundi
- Cameroon
- Congo, Dem. Rep. of
- Rwanda

Region 8: West Africa WADA

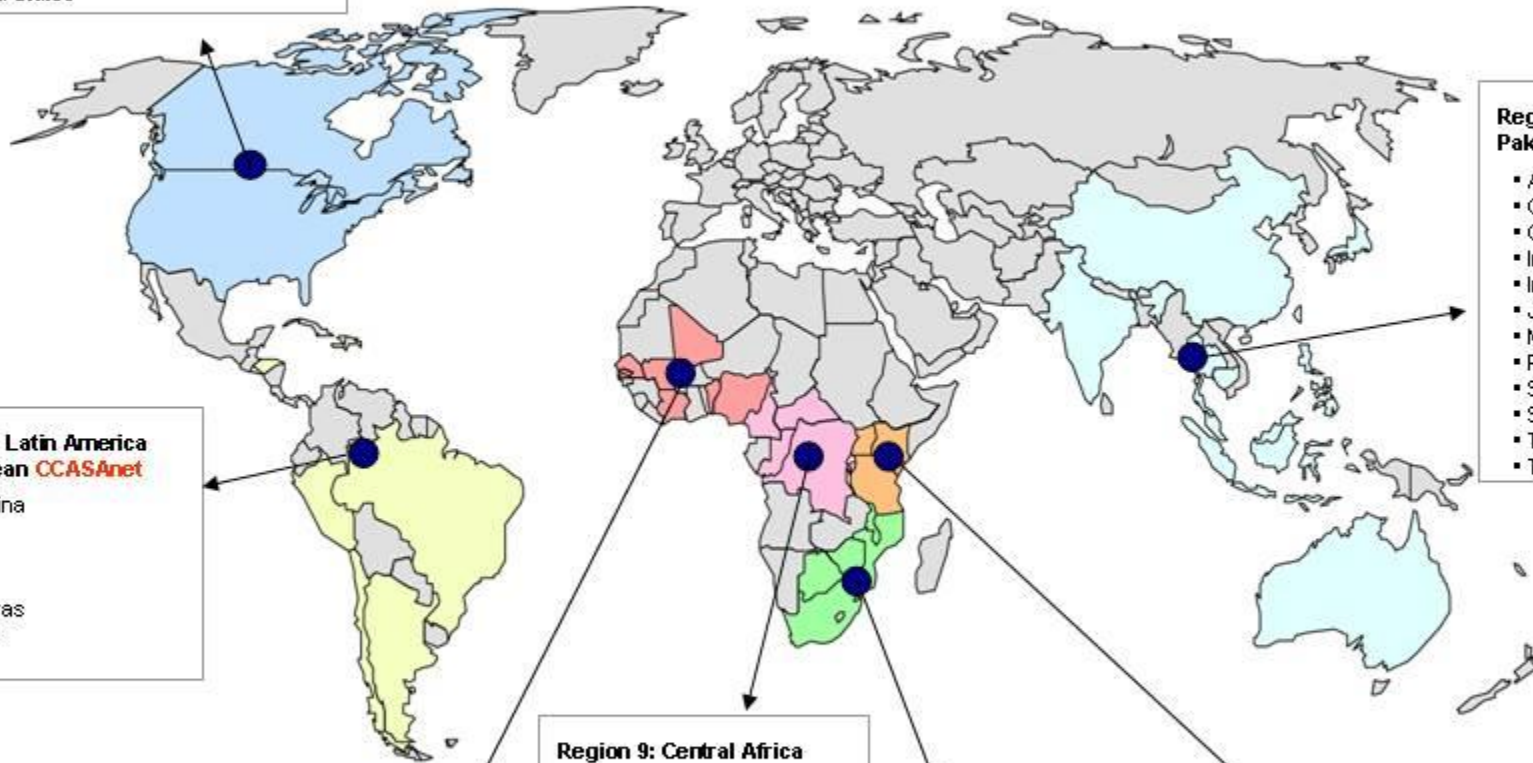
- Benin
- Burkino Faso
- Cote d'Ivoire
- Gambia
- Ghana
- Mali
- Nigeria
- Senegal

Region 11: Southern Africa OASIS

- Botswana
- Malawi
- Mozambique
- South Africa
- Zambia
- Zimbabwe

Region 10: East Africa REACT

- Kenya
- Tanzania
- Uganda



(%) of women/girls by site (*moving target*)



International Epidemiologic Databases to Evaluate AIDS

Totals: N=708,956 (377,392; 53% female)

Region 1: North America NA ACCORD

- Canada
- United States

N=114,000 (Adults only)
Women 16% (18,400)

N=13,215
Female 29% (3889)

Region 5: Australia, India, Pakistan, Asia APHOD

- Australia
- Cambodia
- China
- India
- Indonesia
- Japan
- Malaysia
- Philippines
- Singapore
- South Korea
- Taiwan
- Thailand

N=12,957
Female 40% (5182)

Region 2: Latin America & Caribbean CCASAnet

- Argentina
- Brazil
- Chile
- Haiti
- Honduras
- Mexico
- Peru

Region 8: West Africa WADA

- Benin
- Burkino Faso
- Cote d'Ivoire
- Gambia
- Ghana
- Mali
- Nigeria
- Senegal

N=37,348
Female 61% (22,730)

Region 9: Central Africa

- Burundi
- Cameroon
- Congo, Dem. Rep. of
- Rwanda

N=17,722
Female 67% (11,811)

N=314,600
Female 61% (192,564)

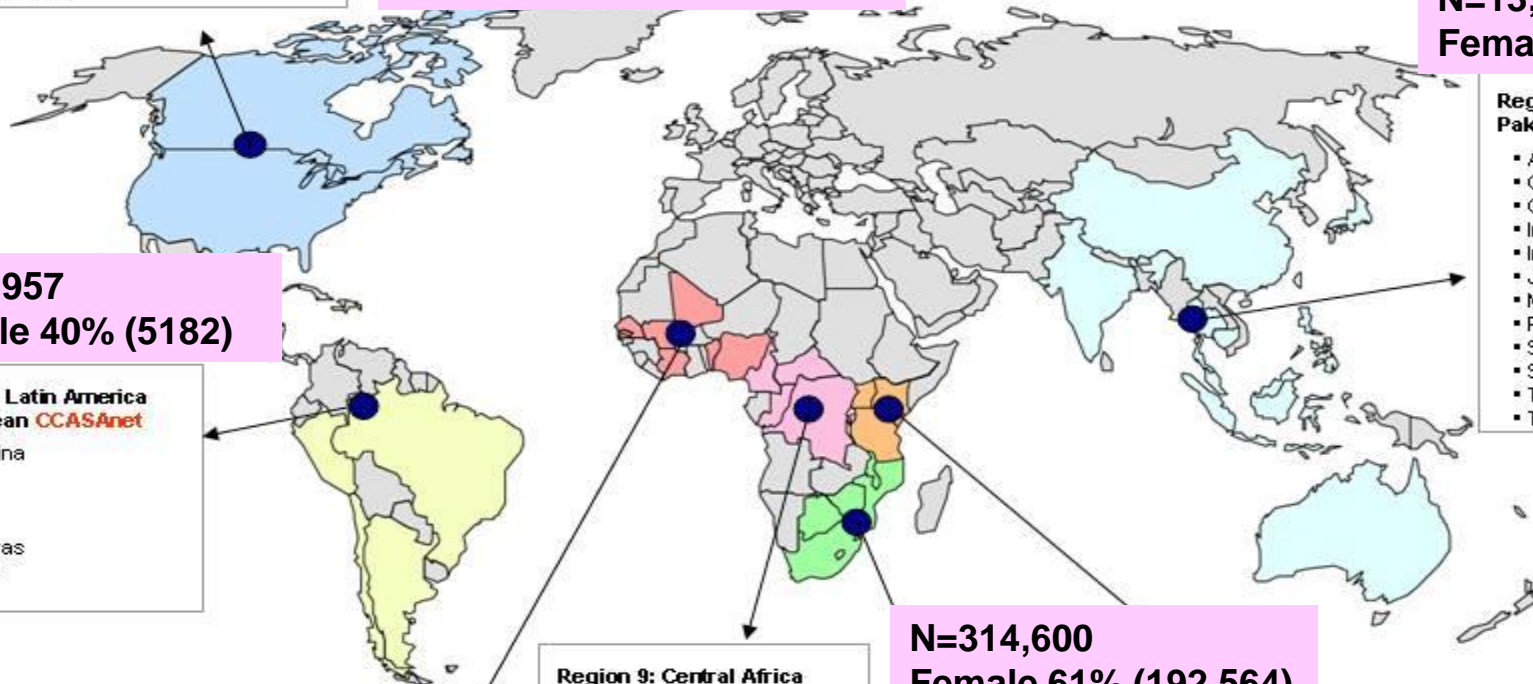
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N=199,114
Female 62% (122,716)





ART-LINC (now ended)



- **Antiretroviral therapy in low income countries (Office of AIDS Research, NIAID, and ANRS)**
- **46% (2976) treatment naïve women; 5% (31) treatment-experienced women**



CNICS

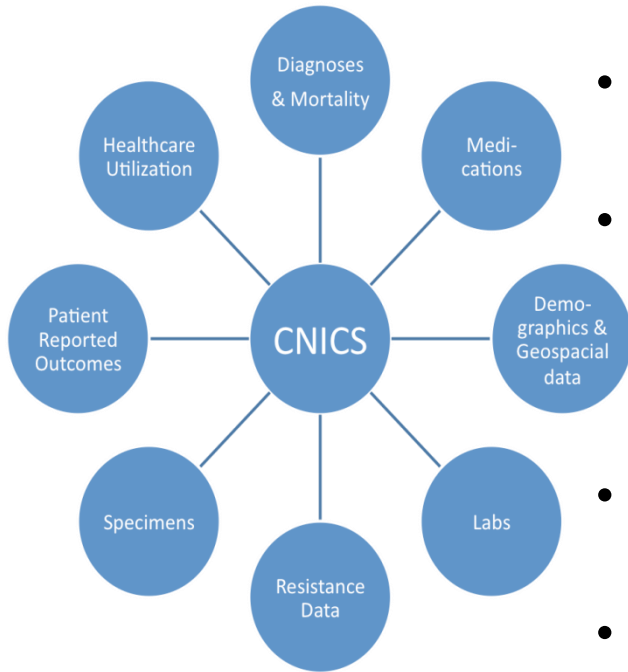
CFAR NETWORK OF INTEGRATED CLINICAL SYSTEMS



Overview of CNICS

- **Links data and specimens from specific Center for AIDS Research (CFARs) US sites via electronic health records into a single research database.**
- **Established in 2002 (has grown from 4 to 8 sites since 2006)**
 - First national CFAR seed funding, now supported by NIH R24
- **CNICS data and specimens are available to *any investigator* who desires to use the platform**
 - Emphasis on mentoring of junior investigators
 - Biostatistical support
- **Establishment of a high quality clinical database**
 - Patient reported outcomes, labs including resistance
 - Specimen repository, including cells

CNICS Sites

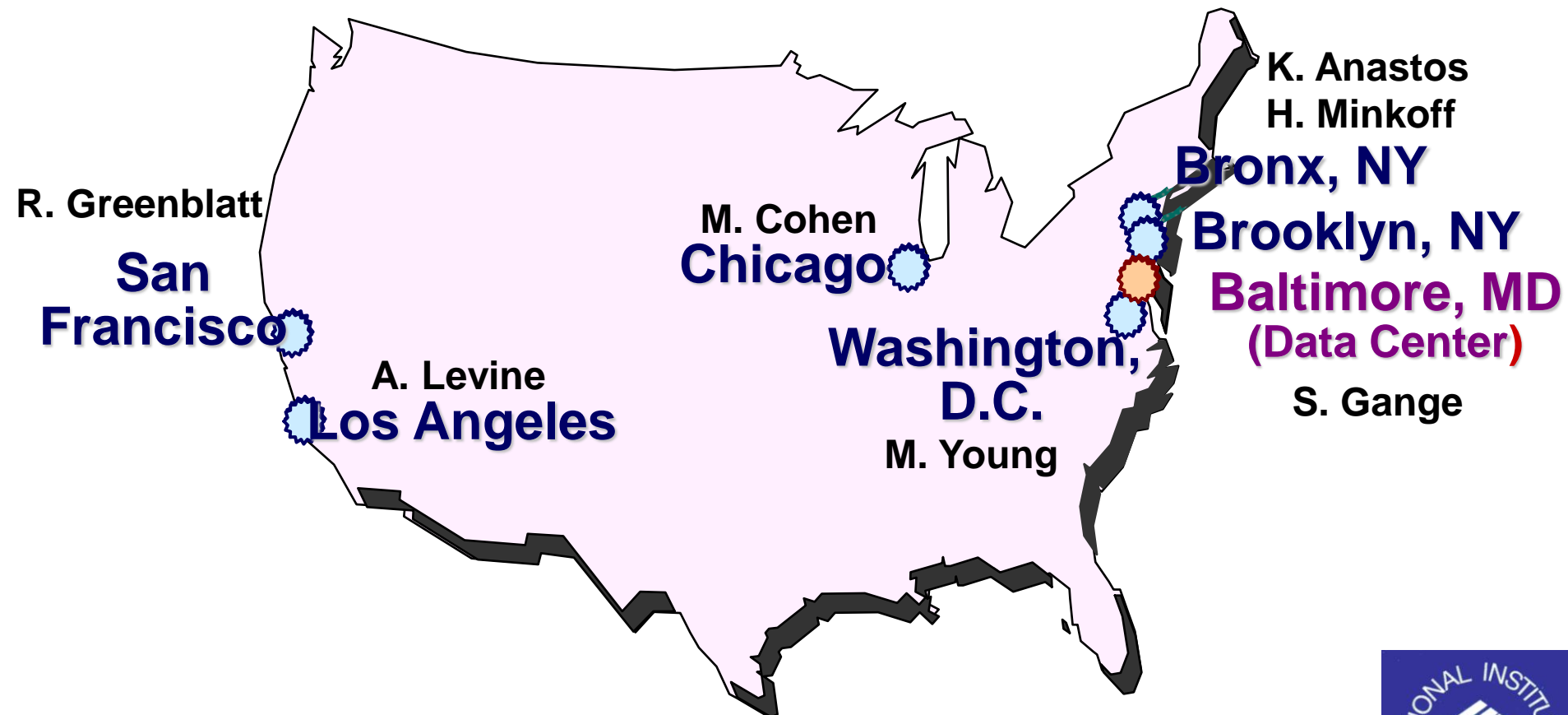


- **University of Alabama at Birmingham (UAB)**
 - **National PI: Michael Saag/Site PI: Michael Mugavero**
- **University of California at San Francisco (UCSF)**
 - **Site PI: James Kahn**
- **University of Washington (UW)**
 - **Site PI: Mari Kitahata**
- **Case Western Reserve University (CWRU)**
 - **Site Leader: Benigno Rodriguez**
- **Brown University CFAR (Fenway)**
 - **Site Leader: Steve Boswell**
- **University of California, San Diego (UCSD)**
 - **Site Leader: Chris Mathews**
- **University of North Carolina at Chapel Hill (UNC)**
 - **Site Leader: Joseph Eron**
- **Johns Hopkins University (JHU)**
 - **Site Leader: Richard Moore**

CNICS Cohort as of Dec 2010

Total		22317	
Male		18028	81%
Female		4289	19%
White		10191	46%
Black		8661	39%
Hispanic		2386	11%
Other		927	4%
HIV Transmission Risk			
MSM		10575	48%
Injection drugs		2975	13%
Heterosexual		5150	23%
Other		2093	9%
Region			
East		6341	28%
South		4293	19%
Central		1665	8%
West		10018	45%

Women's Interagency HIV Study (WIHS)





History of WIHS

- Initiated August 1993 to study natural history, laboratory, clinical, behavioral impact of HIV among U.S. women
- Largest cohort of dedicated cohort of HIV-infected women worldwide (+risk-matched HIV-negative controls)
 - As of March 2010, 3766 participants
 - 2791 (74%) HIV-positive; 975 (26%) HIV-negative
- Re-enrollment 2001-2002
- Currently discussing “replenishing”
- Sponsored by NIAID, NIDA, NICHD, NCI, NIDA, NCRR
- Semi-annual visit (interview-administered questionnaires, physical exam, specimen collection)



Areas of Focused Scientific Research in the WHS

- **Behavior & Substance Use**
- **Cancer**
- **Cardiovascular Disease**
- **Epidemiology**
- **Genetics**
- **Hepatitis / Liver Disease**
- **Human Papillomavirus**
- **Menopause & Aging**
- **Metabolics & Renal Disease**
- **Neurocognition**
- **Pathogenesis**
- **Pharmacokinetics & Antiretroviral Exposure**





Pediatric HIV/AIDS Cohort Study

&

NISDI: NICHD International Site Development Initiative





Two cohorts

- **SMARTT: Surveillance Monitoring for ART Toxicities Study in HIV-uninfected Children Born to HIV-infected Women**
 - From WITS (longitudinal 1990-2006 -public dataset, limited specimens)
 - HIV & ART-exposed, but uninfected children (~half female)
 - Estimate incidence of conditions and diagnoses related to *in utero* exposure or within 1st 2 months of life to ART
 - *Static* (closed, 1240 participants <12 years) & *Dynamic* Surveillance Cohorts: Total ~2300 HIV-exposed/uninfected infants & children w/ 200-300 new infants enrolled/yr (Caregivers also enrolled, mostly HIV-infected women)
- **AMP: Adolescent Master Protocol**
 - ~450 children (~half female) born to HIV-infected mothers
 - Comparison -227 perinatally exposed, HIV-infected children
 - Define impact of HIV & ART on pre-adolescents and adolescents with perinatal HIV

NISDI: *NICHD International Site Development Initiative*

- **Similar to PHACS, with 2 protocols**
- **Prospective, observational study of HIV-exposed & HIV-infected children at clinical sites in Latin American and Caribbean countries (~half female)**
 - **LILAC/Perinatal - 500 HIV-exposed/uninfected infants & children**
 - **PLACES/Pediatric - 500 perinatally HIV-infected infants & children (and database of ~1000 perinatally HIV-infected & ~800 exposed/uninfected)**



Cohorts in clinical trial networks

• NIH-funded cohorts

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- **Microbicide trials network**
 - **MTN-015: *Observational Cohort of Women following HIV-1 Seroconversion in Microbicide Trials***
 - **Observational study of HIV progression and treatment response in HIV+ women formerly enrolled in an MTN trial who had been using a topical microbicide or oral ARVs (as PrEP) when infected**
 - **MTN-016: *HIV Prevention Agent Pregnancy Exposure Registry***
 - **Prospective observational cohort of prevention agent (microbicide) and control group exposures in pregnancy**
- **ALLRT: *AIDS Clinical Trials Group Longitudinal Linked Randomized Trials***
 - **Participants in randomized trials of ART in ACTG followed beyond end of study**
 - **As of June 2010, ~17% (728) women (1.8-6.8 years)**



- **IMPAACT P0174: *A prospective surveillance study of long term outcomes in HIV-infected females, infants, children and adolescents***
 - **Follow up protocol to PACTG 219/219C. Annual chart abstraction. 900 enrolled to date (~half female) with current target ~2000 (no new specimens, visits, not enrolled in PHACS AMP)**
 - **Identify possible long-term adverse outcomes of HIV & complications of ART and experimental interventions in HIV-infected infants, children and adolescents at IMPAACT sites in the U.S.**
 - **P1074 linked with other databases to detect signals of adverse events (and enable focused sub-studies)**

Cohorts in multiple other locations

• NIH-funded cohorts

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- Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS)
- Women's Interagency HIV Study (WIHS)
- Pediatric HIV/AIDS Cohort Study (PHACS)
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...

• Everything else

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- Canada
- Australia
- Latin America
- Africa
- India



European collaborative cohorts

COHERE

SWISS

HIV

COHORT
STUDY

ART

Cohort Collaboration

D:A:D
STUDY



EuroSIDA



ATHENA

Collaborative
HIV
Paediatric
Study

European/ Australian/Canadian/ other cohorts

Cohort	Description	(% and n female)
ANRS: French Hospital Database on HIV	HIV-infected pts in 62 French teaching hospitals	118,147 (32%; 37,807 women)
ART-CC: ART Cohort Collaboration	19 cohort studies from Europe and North America of patients on ART	74,048 (26%; 18,924 women)
D:A:D: Data Collection on Adverse Events of Anti-HIV Drugs	Multinational cohort collaboration (Europe, USA, Australia)	35,441 (24%; 8,506 women)
Swiss HIV Cohort Study	Observational study of HIV-infected patients in Switzerland	12,500 (29%; 3,625 women)
EuroSIDA	Prospective cohort, 80 clinics in 30 European countries and Argentina	11,243 (22.9%, 2,575 women)
I.Co.N.A: Italian Cohort Naïve from ARVs	Prospective cohort in Italy of HIV-positive patients naive to ARVs	5,869 (30.3%; 1,778 women)
CASCADE: Concerted Action on Seroconversion to AIDS & Death in Europe	Pooled data, 22 cohorts of HIV pts w/ known seroconversion Dates, Europe, Australia, Canada	8332 (19%; 1,583 women)
Royal Free Cohort	All HIV-positive patients in Royal Free Clinic, London, UK	3,661 (21.1%; 772 women)
CHIPS (Collaborative HIV Paediatric Study Cohort)	Children presenting with HIV and infants born to HIV-infected mothers in UK and Ireland	627 (50%; 312 girls)

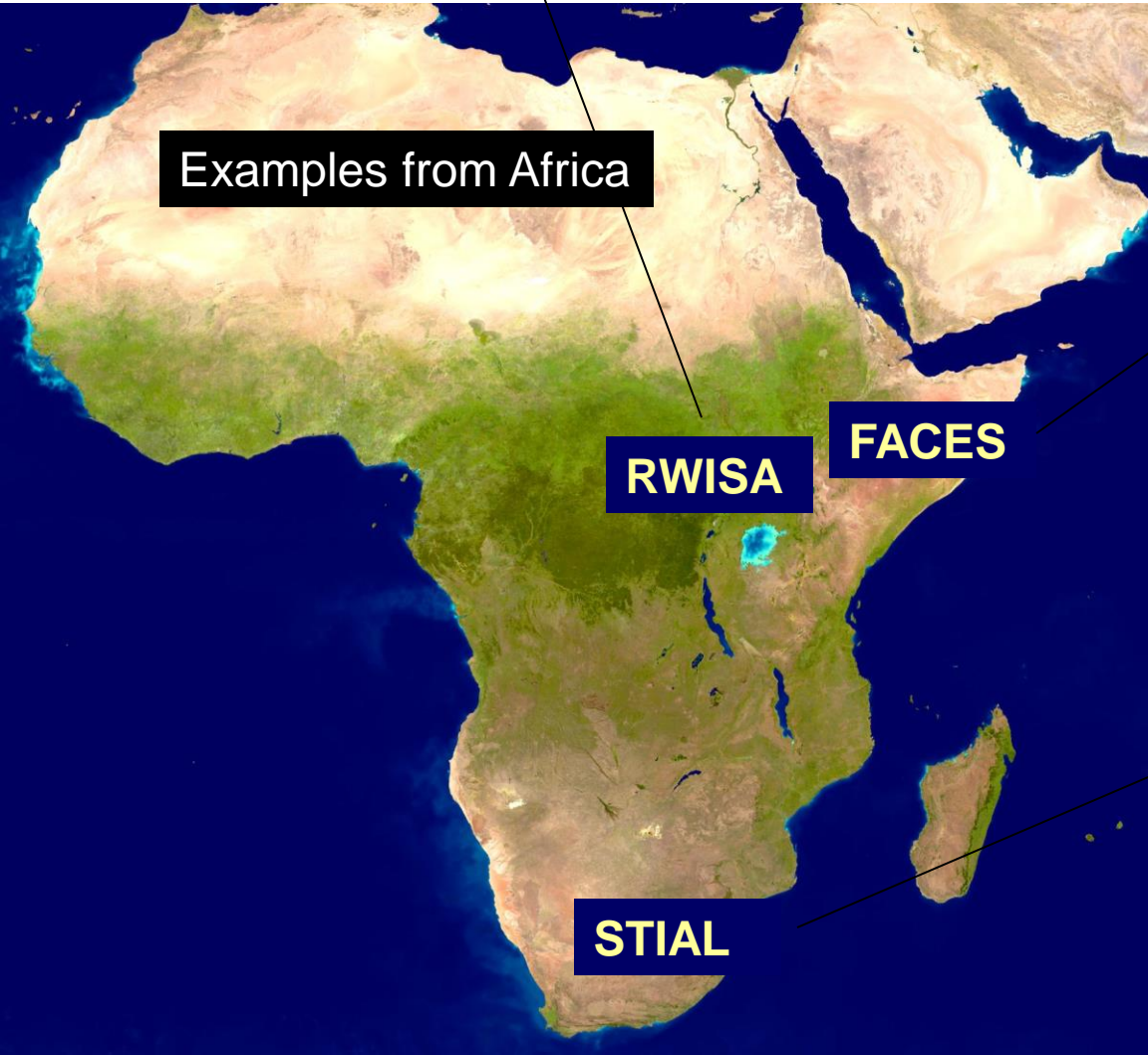


Examples from Latin America

Caribbean Central and South America (CCASA-net), region 2 leDEA	n= 12,957 (40% female)  CCASA net
NICHD International Site Development Initiative (NISDI)	n= 2,800 (50% girls)
Chilean AIDS Cohort (P. Vasquez)	n = 5,120 (16% women)
Rapid II study group: 7 Latin American countries; Pts enrolled to study metabolic and CVD.	n= 4010 (26% women)
LATINA cohort: Retrospective cohort – Brazil (1); Mexico (1); Peru (1); Argentina (5)	n= 6007 (30% female) 



Rwandan Women's Inter-association and Assessment: Originally funded by NIH supplement '04; building research capacity and informing clinical care. 936 women (76% HIV+)



Family AIDS Care and Education Services (Kenya): PEPFAR-funded HIV care and treatment program with cohort for research (88,000; 65% women).



South African Test, Identify and Link: Prospective cohort from 2 sites in KwaZulu-Natal (one Durban, McCord Hospital); 2777 pts (49% women)

Examples from India





Sex specific findings from cohorts: Outcome trends improving in women

1987  2009

Differential use of ARVs
Unknown infection date
Differential access to care
Differential provider treatment
Social factors
Higher rates of IVDU

Higher uptake of ARVs (IVDU Spain)
?Lower viral load & higher CD4
?Higher drug levels
Higher baseline life expectancies
?Better cardiovascular outcomes
?Less viral resistance

Better outcomes in women

Same in men and women

Worse outcomes in women

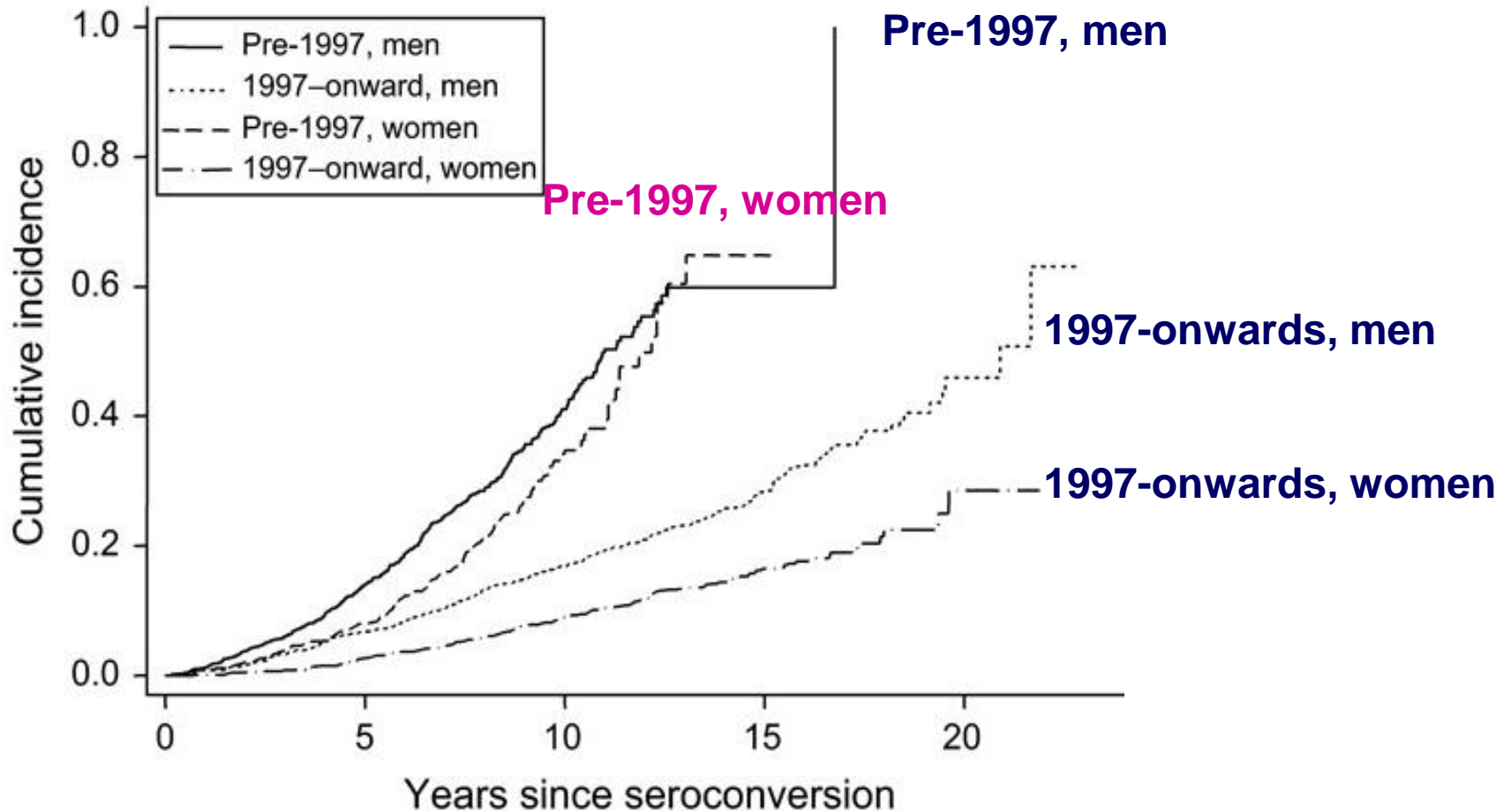
Rothenberg 1987; Reeves 1988
Friedland 1991; Lemp 1992; Melnick 1994

Cozzi Lepri 1994; Chaisson. 1995
Brettelle 1996; Prins 1999
Pezzotti 1999; Junghans 1999
Sterling 2001; Lewden 2001; Gebo
2003; Porter 2003; Moore A 2003;
Perez-Hoyos 2007

Moore A. 2002; Perez-Hoyos. 2003
CASCADE 2003; Garcia de la Hera.
2004; Nicastri 2005; Jarrin I. 2007;
Nicastri 2007; Collazos 2007

CASCADE cohort:

AIDS and death rates lower in women in HAART era



Reasons for mortality differ by sex in the U.S.

- Comparison study of causes of mortality in Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS)¹
- Higher rates accident or injury-related mortality in women vs men (2.96 vs. 0.79/1000; OR 1.88 (1.13-3.16), p 0.016)
- Risk factors for death varied by gender

WOMEN

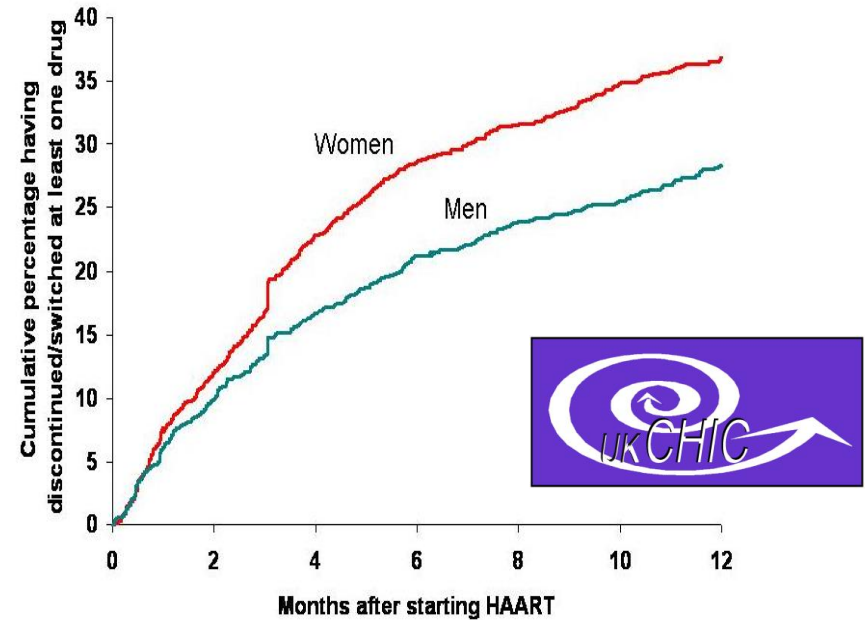
- Decreased CD4 (p 0.047)
- Unemployment (p 0.023)
- Higher etoh use (p 0.002)
- IVDU (p < 0.001)

MEN

- Higher education (p 0.009)
- Depression (p 0.001)
- Higher # sex partners (p 0.036)

Cohorts (and clinical trials – GRACE⁸, CASTLE⁶) – show more treatment discontinuation in women

- UK Collaborative HIV Cohort (CHIC)⁹
- I.Co.N.A.
- Swiss Cohort Study
- Royal Free Clinic
- CASCADE



¹Murri. JAIDS 2003; ²Elzi. Arch Intern Med 2010; ³Toulami (CASCADE) JAIDS 2006; ⁴Smith JAIDS 2007; ⁴Losina. CID 2010; ⁵Smith. JAIDS 2007; ⁶Johnson. Gender-based differences in antiretroviral-naïve patients treated with ritonavir-boosted protease inhibitors: results from the CASTLE study through 96 weeks. 12th European AIDS Conference, 2009; ⁷Bhattacharya. JAIDS Oct 2010; ⁸Currier J et al. Sex-based outcomes of darunavir-ritonavir: A single group trial. Annals of Internal Medicine 2010: 153(6); ⁹Barbar T and... Sabin C.. European AIDS Clinical Society; 2009

Other cohorts in the workshop's “cohort session”



Longitudinal Investigation into
Supportive & Ancillary Health Services



ISIS
a women's study



Chilean AIDS Cohort Study

stop aids. make the promise.
Don't turn your back on AIDS.

STOP AIDS.
Make the Promise.

Each of us can help stop the spread of HIV and reduce the impact of AIDS.
You don't have to be a top scientist working on a cure to make a difference.
Protecting yourself and others from HIV infection, welcoming someone living
with HIV into your life or even just talking about HIV and AIDS can help.
Are you taking action?

Make your promise now at www.worldaidscampaign.org

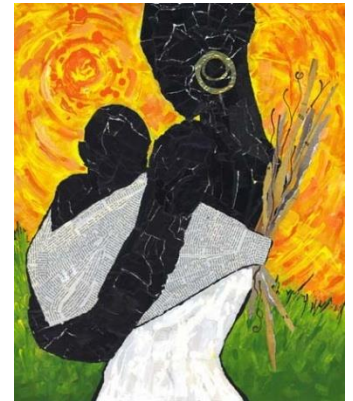


Concept: Manohar Singh, network: kumarasingh@net



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- **WIHS: Stephen Gange**
- **European Cohorts: Caroline Sabin**
- **ACTG: Judith Carrier**
- **leDEA PIs**
- **African cohorts: Kathy Anastos, Ingrid Bassett, Elizabeth Bukusi**



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