

# Sex Differences in HIV Cure Research & Status of Women's Participation in Current Cure-Related Studies

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# Overview

- Part 1: Sex differences in HIV Cure Research
  - Current knowledge
  - Knowledge gaps
- Part 2: Status of Women's Participation in Current Cure-Related Studies
  - Overview of 2019 cure-related landscape
  - Demographics of current cure landscape

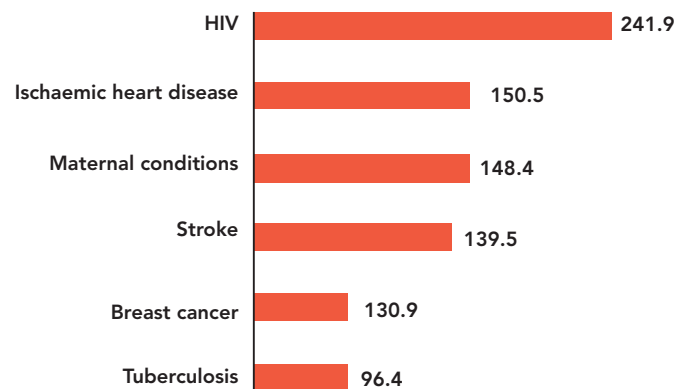
# Acknowledgements

- Eileen Scully, Sara Gianella, Katy Godfrey, Richard Jefferys, Danielle Campbell, Karine Dube
- Treatment Action Group, ACTG, Women's HIV Research Collaborative, ATAC

# **PART 1: SEX DIFFERENCES IN HIV CURE RESEARCH**

# The global burden of HIV infection in women and girls

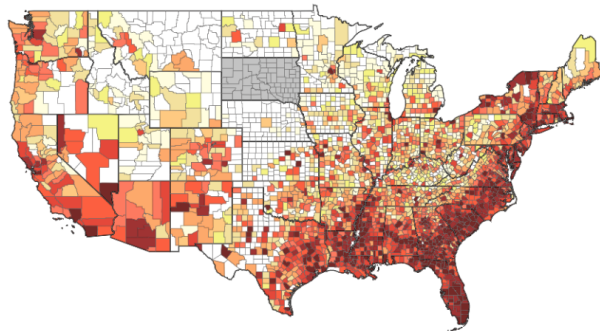
- 18.8 million women and girls
- AIDS-related illnesses: leading cause of death among women and girls ages 15-49
- Young women are 2x as likely to acquire HIV
- 3 of 4 new infections in 15-19 year-olds in Sub-Saharan Africa are in girls



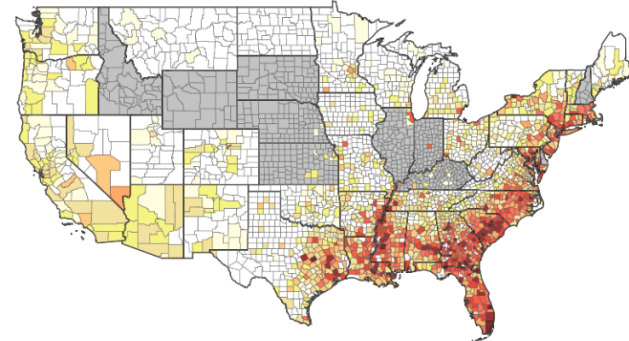
# HIV infection in women: data from the U.S. and Baltimore

- United States women account for
  - 20% of cumulative AIDS diagnoses
  - 23% of those living with HIV
- Baltimore women are 34.3% of people living with HIV

Prevalence of HIV



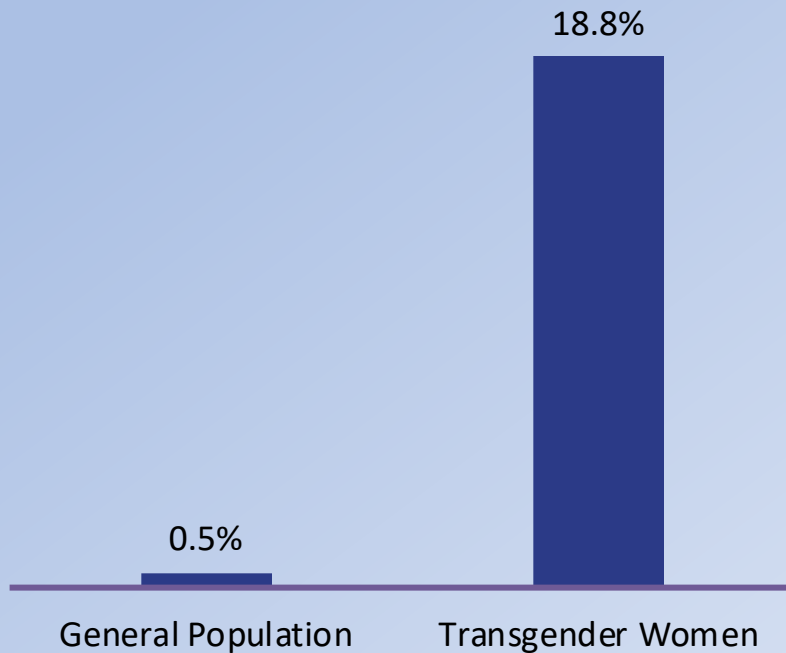
Prevalence of HIV among Women



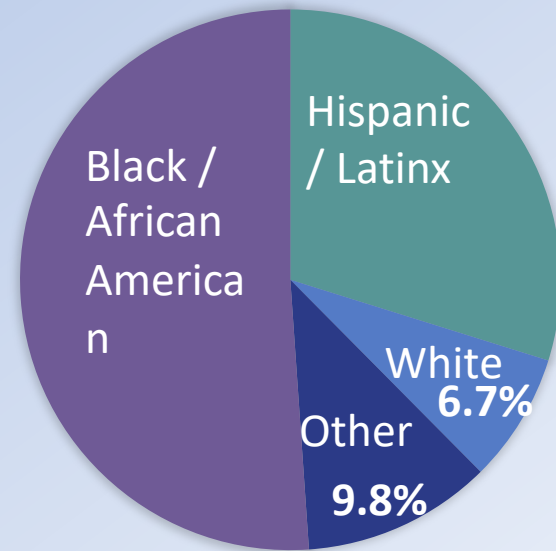
Sources CDC, 2016 data;  
AIDSvu.org

# Transgender Women & HIV in the US

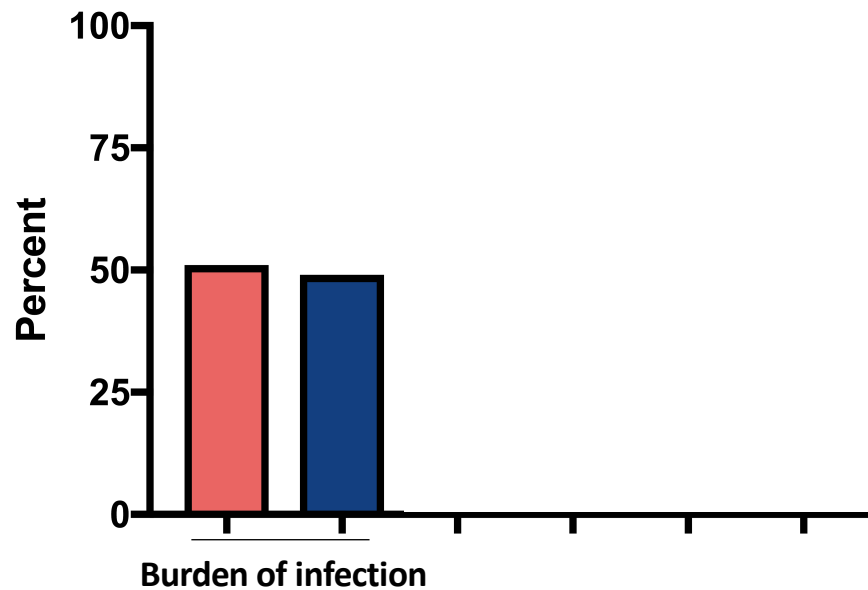
US HIV PREVALENCE



HIV PREVALENCE BY RACE/ ETHNICITY:  
US TRANSGENDER WOMEN



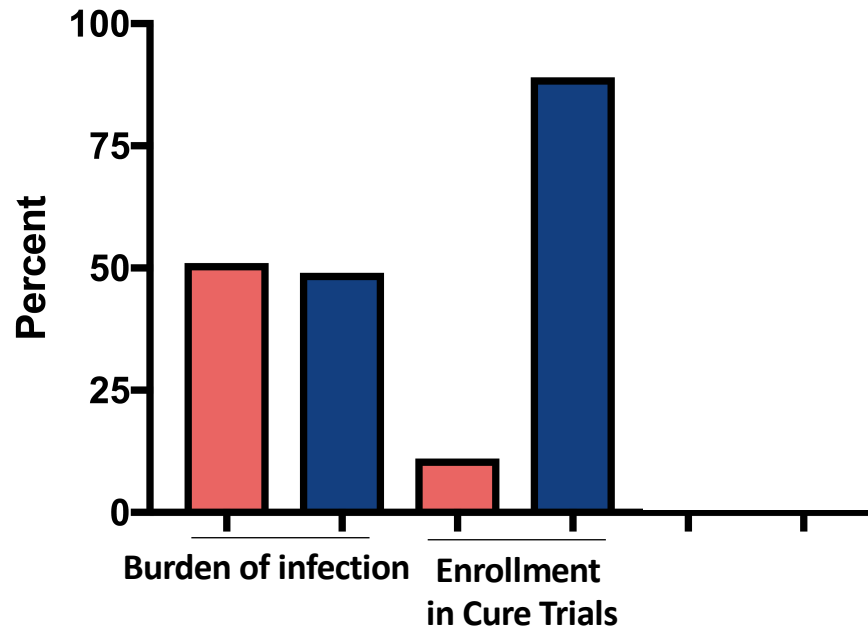
# HIV Cure: the relevance of biological sex



Johnston and Heitzeg, AIDS Res and Human Retroviruses, 2015

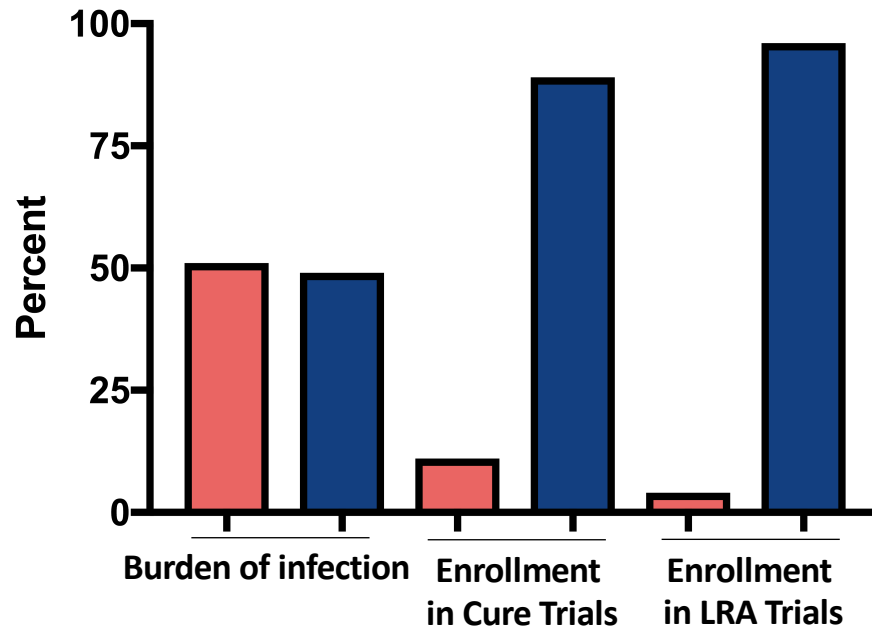


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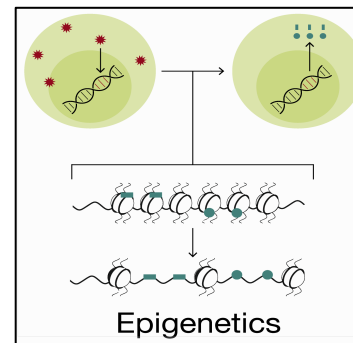
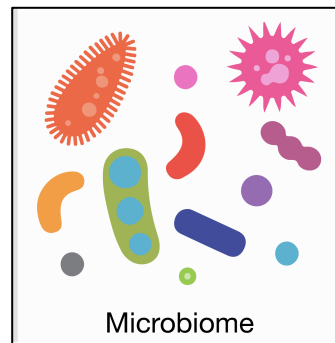
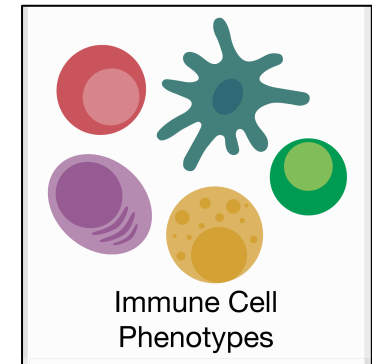
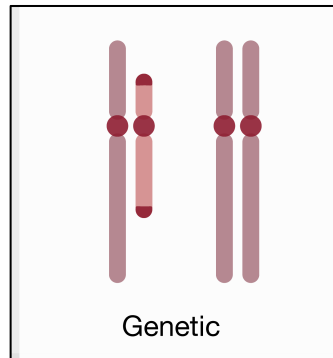
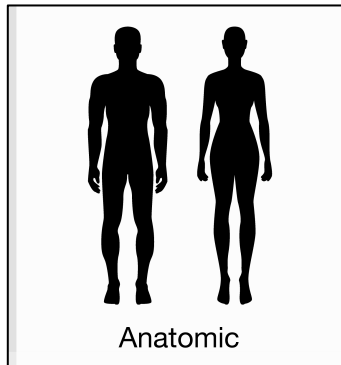
Johnston and Heitzeg, AIDS Res and Human Retroviruses, 2015

# HIV Cure: the relevance of biological sex



Johnston and Heitzeg, AIDS Res and Human Retroviruses, 2015

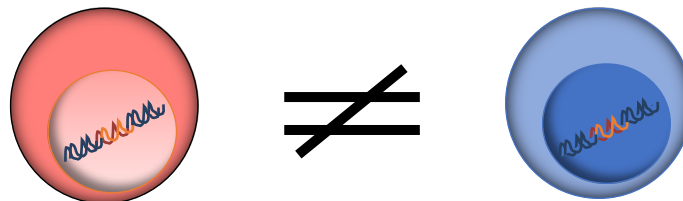
# Biological determinants of sex differences



Scully, E *Curr HIV/AIDS Reports*, 2018

# Sex differences in HIV cure research

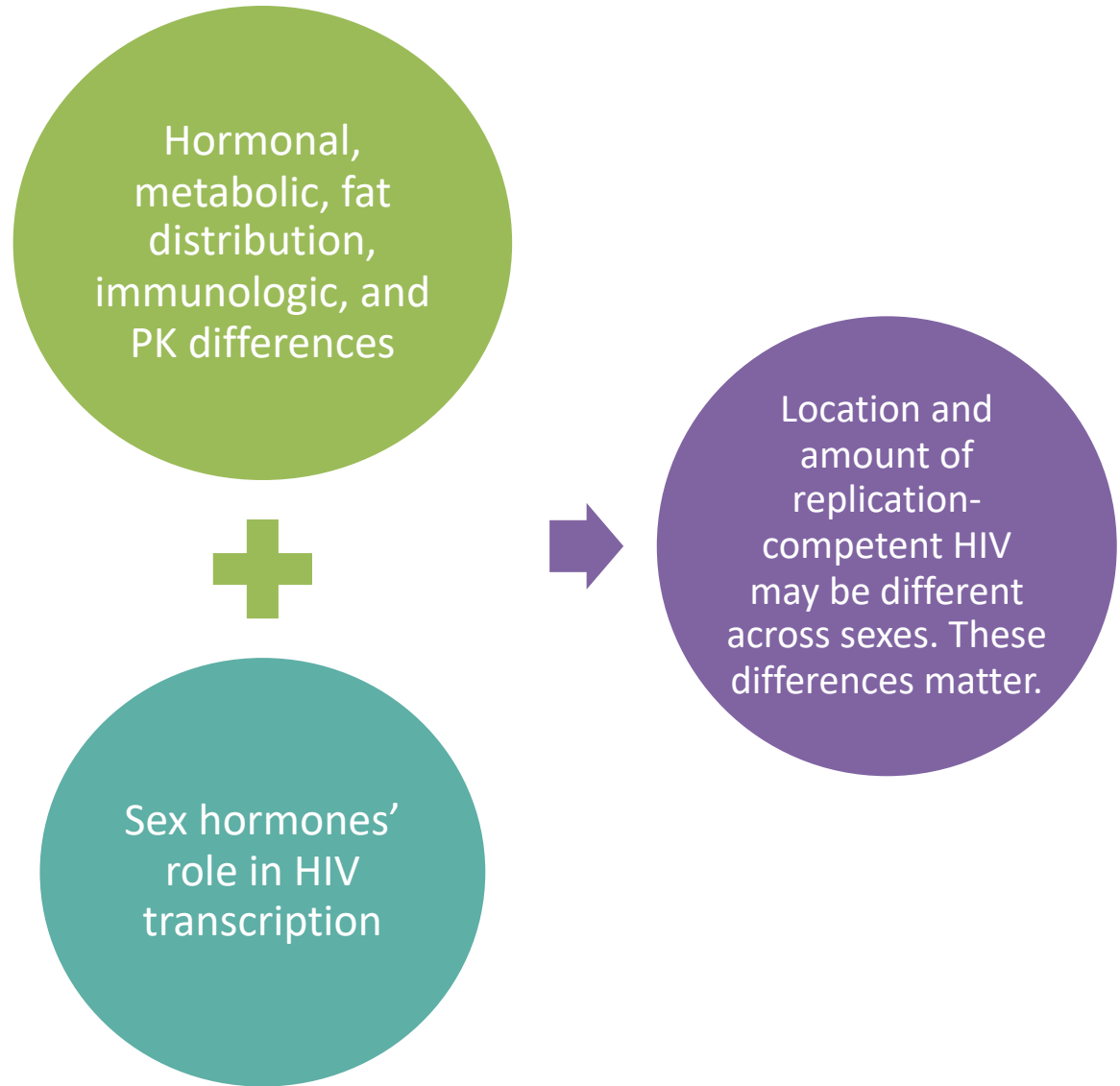
- Measured differences in
  - Markers of viral persistence
  - Relationship to T cell parameters
  - Transcriptional controls
- Therapeutic targets:
  - *Host* transcriptional machinery
  - *Host* immune response



# Differences in immune pathogenesis

- X and Y chromosomes have different genes on them; and play a role in immune response
- Hormones (like estrogen or progestins) play a role in immune response.
- We need to know more about the role of sex hormones and how they relate to cure strategies

# Differences in HIV reservoirs in tissues and anatomic compartments



# Female genital tract

- FGT is complex
- Relationship between the amounts of replication-competent HIV in blood and in the female reproductive tract is unknown
- Evidence for virus production in the female genital tract when HIV RNA levels are undetectable in blood plasma
- Takeaway: each part of FGT has a role in maintaining HIV reservoirs (and immune activation and HIV progression), but we just don't know enough yet to say what exactly this effect is.

# Vaginal and Neovaginal microbiomes

- Vaginal microbiome plays a role in risk of HIV acquisition and transmission (as well as STIs and other infections and diseases)
  - Variation in composition across life course and during reproductive transitions
- Limited knowledge about neovaginal microbiome
  - Variation in composition depending on source



# Additional considerations for cure research with women

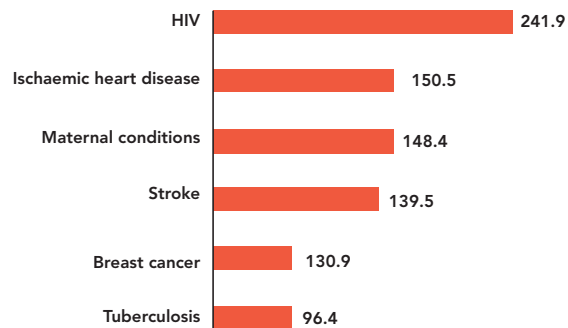
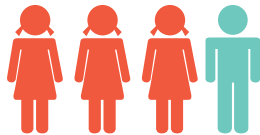
- Collecting sex-specific samples a challenge
  - Pelvic exam adds time, can be inconvenient for participant and provider
  - Need samples throughout menstrual cycle to account for variations
  - Self-collection is an option, but not all women are comfortable with it
- Limited financial climate + pressure to enroll studies quickly = sites often rely on established recruitment practices or draw from the same pools of potential participants

# Barriers to engaging women

- A 2014 survey of ACTG community members found:
  - Competing priorities (33%),
  - Cultural stigma (13%)
  - Lack of appropriate incentives (13%)
  - Lack of education about the clinical trials process (14%)
  - Lack of awareness about trials currently open for enrolment (14%)
  - Unwillingness to serve as a 'guinea pig' (8%)
  - Recruitment strategies lack geographic or demographic diversity (8%)
- We know the issues—now we need to address them!

# Implications

- Overall and sex disaggregated analyses may have novel insights
- Immunomodulatory therapies should be considered in light of sex differential activation of immune pathways (PD-1, TLR7)
- Signatures associated with rebound or reservoir size/activity may differ
- The global burden of infection in women obligates that cure research speaks to sex mediated immunologic differences



## **PART 2: STATUS OF WOMEN'S PARTICIPATION IN CURRENT CURE- RELATED STUDIES**

# 2019 response rate

- Contact made with 133 studies – 73 responded in some way:
  - 5 declined to complete (won't comment on ongoing study (2); results have been published (2); current study is an early stage proof of concept phase 1 study so many of the questions are not applicable)
  - 1 study closed
  - 2 responded that the study isn't really a study
  - 65 completed survey (37 also completed 2018 survey)



- 54.8% response rate (2018 response rate = 57%)

133 studies  
in 24  
categories on  
TAG listing in  
Aug 2019

Adoptive immunotherapy (N=1)

Anti-Proliferative (N=1)

Antiretroviral therapy (N=1)

Combinations (N=17)

Dual-Affinity Re-Targeting (DART)  
Molecules (N=1)

Gene Therapies for HIV-Positive People  
with Cancers (N=6)

Hormones (N=1)

Immune Checkpoint Inhibitors (N=5)

Observational (N=36)

Retinoids (N=1)

Stimulants (N=1)

Toll-Like Receptor Agonists (N=1)

Anti-Inflammatory (N=2)

Antibodies (N=20)

Cannabinoids (N=1)

Cytokines (N=2)

Gene Therapies (N=9)

Gonadotropin-Releasing Hormone  
(GnRH) Agonists (N=1)

Imaging Studies (N=4)

Latency-Reversing Agents (N=4)

Proteasome Inhibitors (N=1)

Stem Cell Transplantation (N=3)

Therapeutic Vaccines (N=7)

Treatment Intensification/Early  
Treatment (N=7)

Projected  
number of  
participants  
by category  
(based on  
registry data)

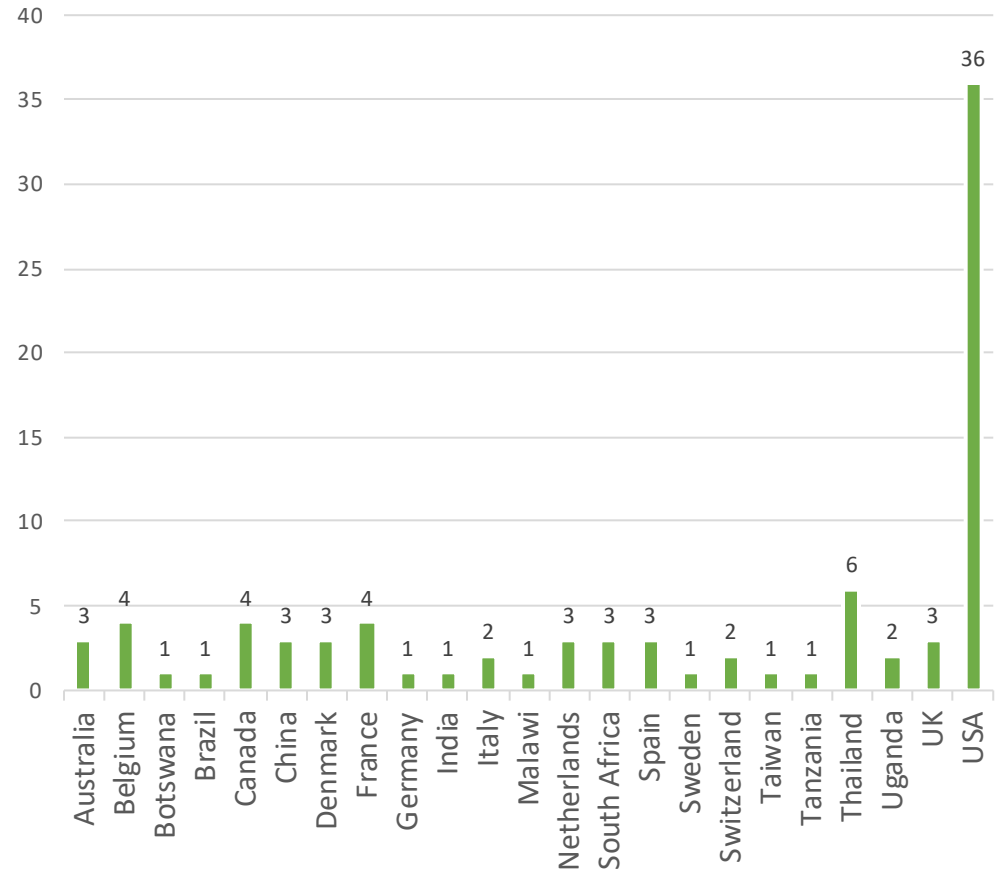
Category	Mean	Median	Range	Total
Adoptive immunotherapy (N=1)	12	--	--	12
Anti-Inflammatory (N=2)	87	87	64 - 110	174
Anti-Proliferative (N=1)	5	--	--	5
Antibodies (N=19)	40	40	8 - 75	767
Antiretroviral therapy (N=1)	40	--	--	40
Cannabinoids	26	--	--	26
Combinations (N=17)	88	34	8 - 905	1,507*
Cytokines (N=2)	15	15	10 - 20	30
Dual-Affinity Re-Targeting (DART) Molecules (N=1)	26	--	--	26
Gene Therapies (N=9)	16	12	6 - 40	152
Gene Therapies for HIV-Positive People with Cancers (N=6)	8	7	3 - 18	51
Gonadotropin-Releasing Hormone (GnRH) Agonists (N=1)	52	--	--	52
Hormones (N=1)	22	--	--	22
Imaging Studies (N=4)	15	14	5 - 30	63
Immune Checkpoint Inhibitors (N=5)	48	45	20 - 96	241
Latency-Reversing Agents (N=4)	29	24	9 - 60	117
Observational (N=33)	252	66	3 - 2550	8,325
Proteasome Inhibitors (N=1)	18	--	--	18
Retinoids (N=1)	12	--	--	12
Stem Cell Transplantation (N=3)	36	25	5 - 80	110
Stimulants (N=1)	10	--	--	10
Therapeutic Vaccines (N=7)	38	40	24 - 60	268
Toll-Like Receptor Agonists (N=1)	28	--	--	28
Treatment Intensification/Early Treatment (N=7)	239	101	60 - 621	1,676*
<b>Total</b>				<b>13,732</b>

# Current enrollment by category

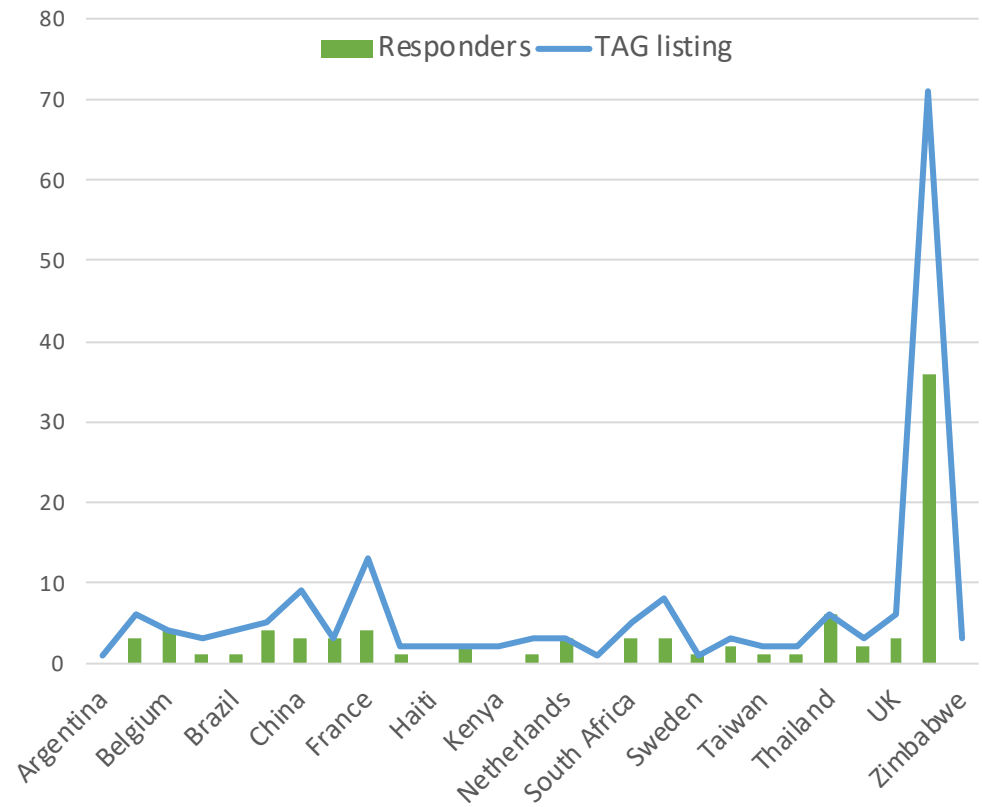
Category	Total enrollment in category	No. of studies in category	Range of enrollment	Range of enrollment (%)
Adoptive Immunotherapy	2	1	N/A	N/A
Antibodies	93	9	3 - 18	7.7% - 83.8%
Combinations	101	6	1 - 50	2.5% - 83.3%
Cytokines	7	1	N/A	N/A
Gene Therapies	13	2	3 - 10	33.3% - 50%
Gonadotropin-Releasing Hormone (GnRH) Agonists	22	1	N/A	N/A
Imaging Studies	15	1	N/A	N/A
Immune Checkpoint Inhibitors	52	3	5 - 39	11.1% - 65%
Latency-Reversing Agents	2	1	N/A	N/A
Observational	1050	5	5 - 624	2.8% - 128%
Stem Cell Transplantation	2	1	N/A	N/A
Therapeutic Vaccines	82	4	7 - 42	20% - 105%
Treatment Intensification/Early Treatment	862	3	58 - 624	78.4% - 120%



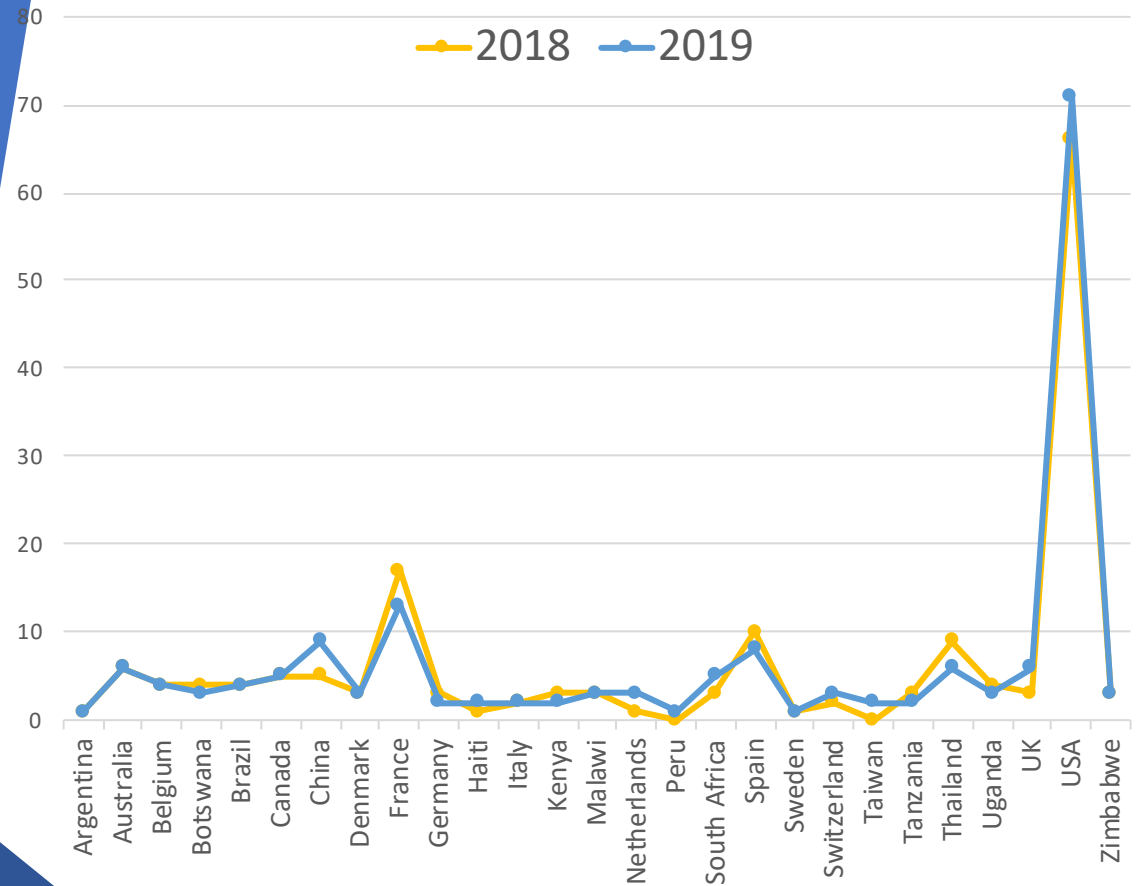
# Location (2019 responders)



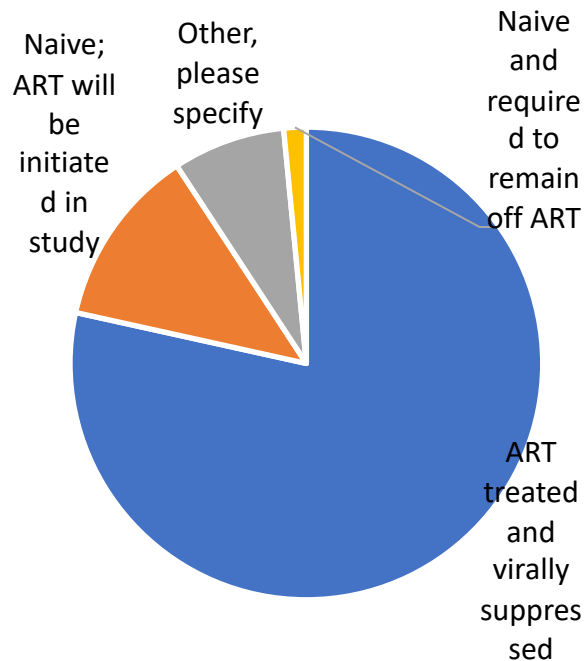
Location  
(2019 all  
trials)



Geographic  
distribution  
of all  
studies  
remained  
stable 2018-  
2019

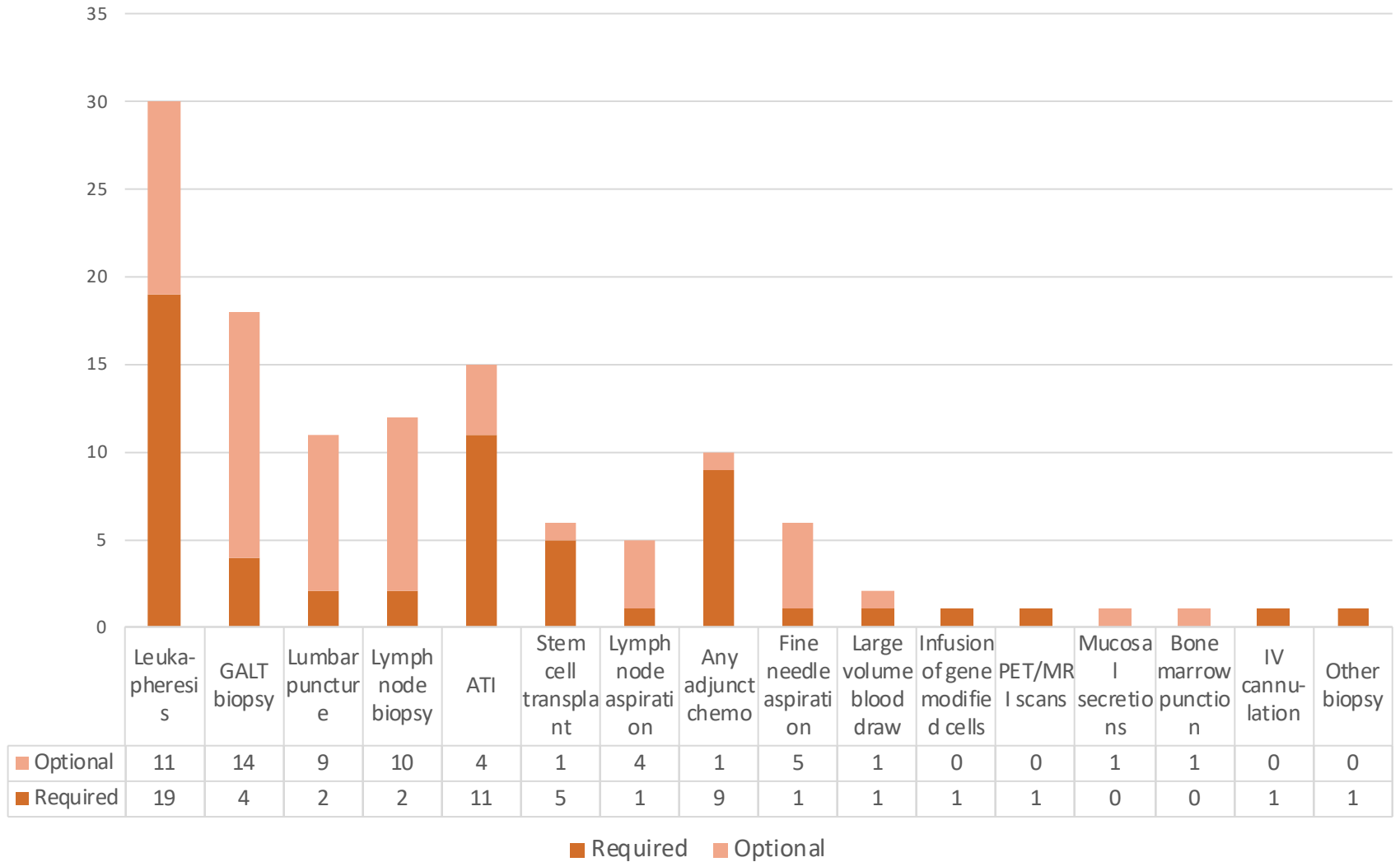


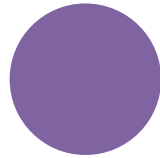
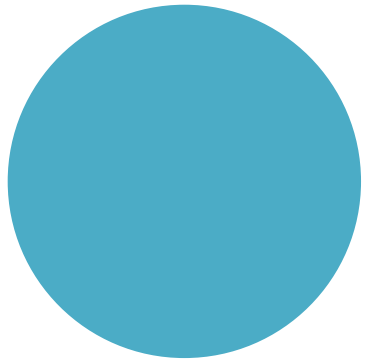
# ART status



- 51/65 (78%) of studies will enroll participants who are ART-treated and virally-suppressed
- 1 study will enroll participants who are naïve and required to remain off ART
- 8/65 (12%) will enroll participants who are naïve and will initiate ART during the study
- 5/65 (7%) have other ART criteria:
  - Two arms – one ART naïve and one ART-treated/virally suppressed
  - Primary HIV infection confirmed
  - Three arms—HIV-negative; ART-treated and virally suppressed; HIV-positive and off ART (naïve or previously treated)
  - Mostly ART-treated/virally suppressed but a few post-treatment controllers
  - Study includes HIV negative participants not administered ART

# Invasive procedures





# DEMOGRAPHICS

2019 responders

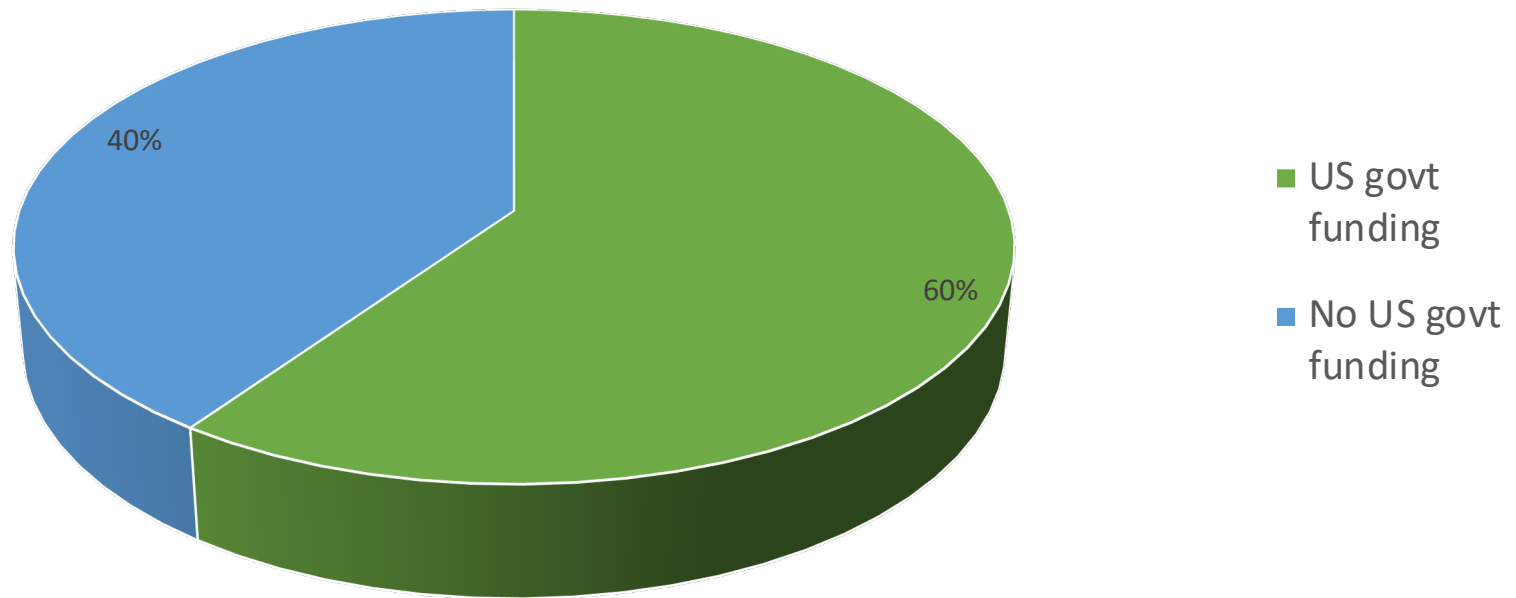
# Relevant US regulations

**NIH Revitalization Act of 1993:** NIH mandate to ensure the inclusion of women and minority groups in all NIH-funded clinical research in a manner that is appropriate to the scientific question under study allows **valid analysis** of whether the variables being studied in the trial affect women and minorities differently.

- Results should be disaggregated and reported by sex
- Applicable to Phase III and pivotal Phase II and IV studies.

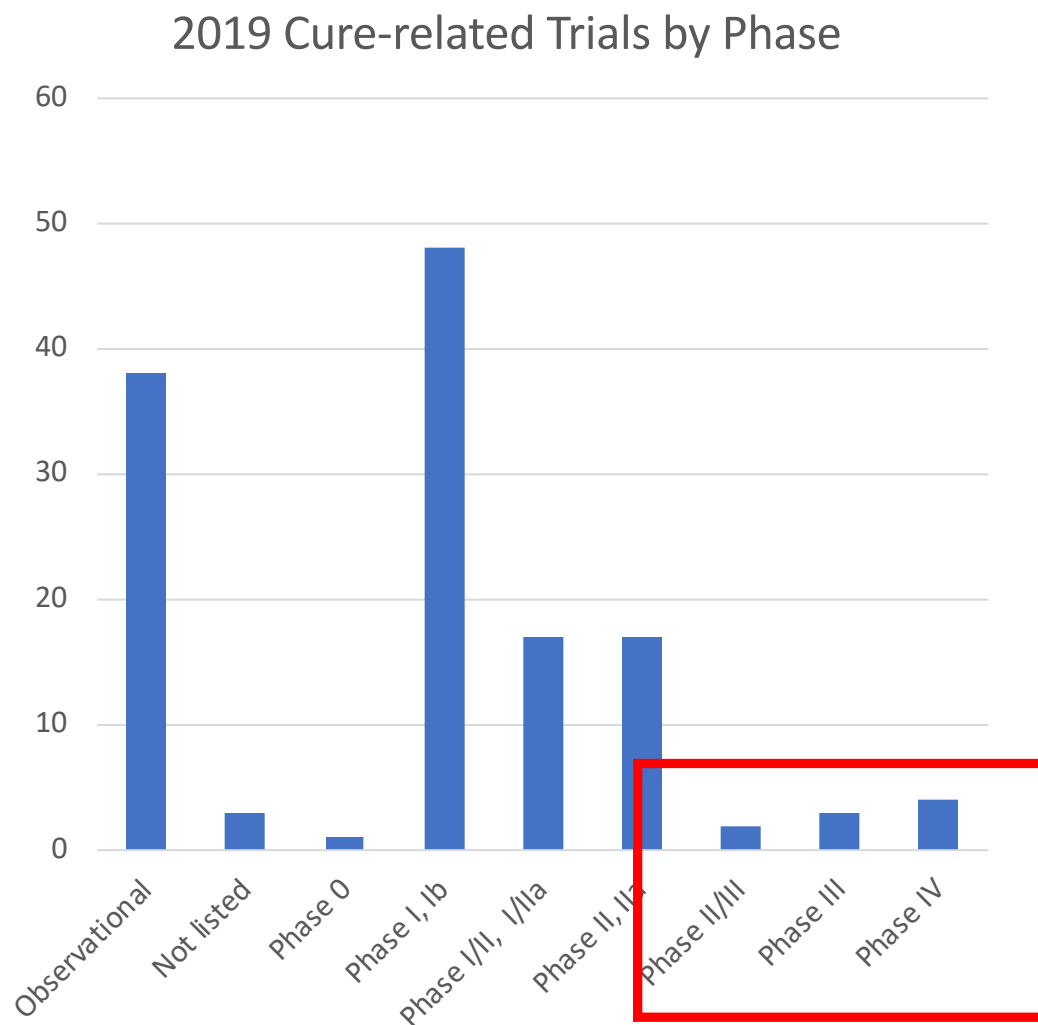
**NIH Sex as a Biological Variable Policy (2016):** “NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.”

Of 2019 responders who indicated funding source for studies (N=67)





Cure-related research largely is largely early-phase (registry data)

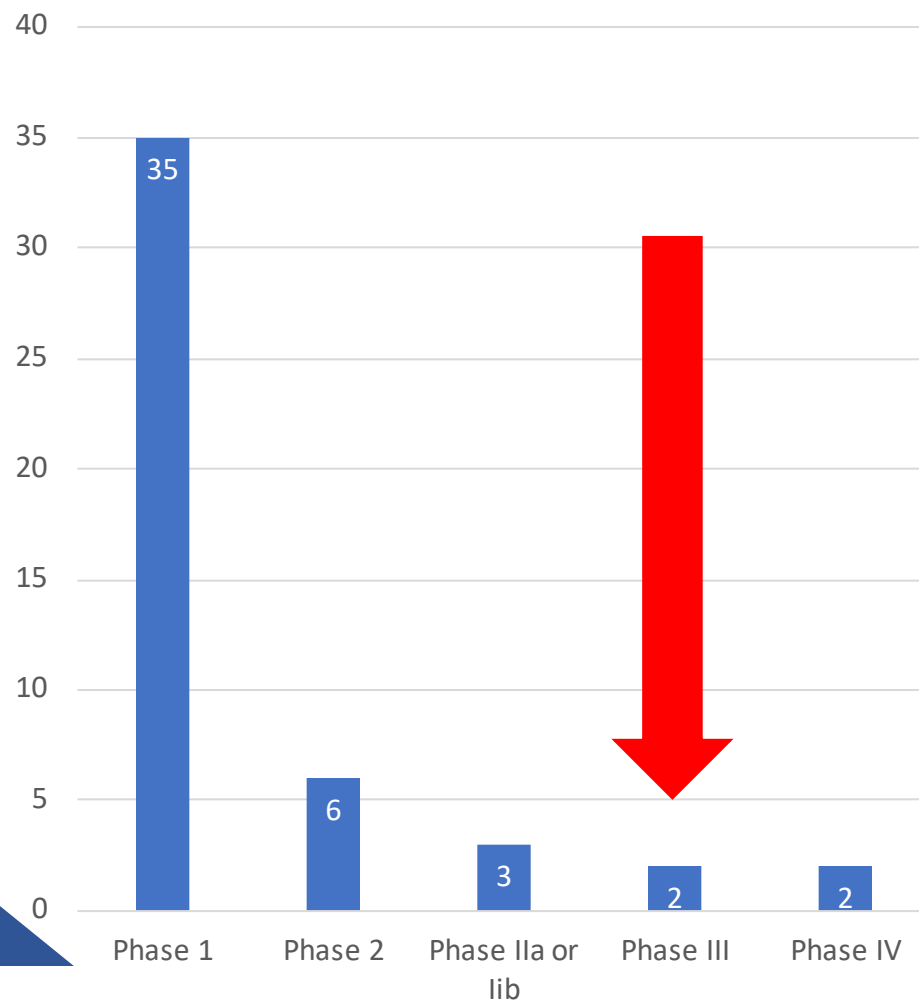


## Demographic targets

- Survey question: Does the study have any of the following demographic targets beyond what is required by inclusion/exclusion criteria?
  - Percentage female (sex)
  - Percentage women (gender)
  - Percentage over 50
  - Percentage of Hispanic descent
  - Percentage of Black/African descent
  - Percentage of Asian descent
  - Other

Categories  
by phase  
(2019  
responders)

2019 Cure-related trials by phase



# Demographic targets

# (%) of respondents reporting

	Sex	Gender	Over 50	Hispanic	Black/ African	Asian	Other
Formal target	4 (6%)	2 (3%)	0 (0%)	1 (1%)	3 (5%)	0 (0%)	1*
Informal target	11 (17%)	6 (10%)	2 (3%)	2 (3%)	3 (5%)	3 (5%)	
No target	48 (76%)	51 (86%)	56 (96.5%)	54 (95%)	52 (89%)	53 (95%)	
Total responses	63	59	58	57	58	56	*Pediatric/ adolescent

# Demographics of current enrollment

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- 60 studies provided information on current enrollment
  - 31 provided information on sex of current participants
  - 20 provided information on gender of current participants
  - 20 indicated if any participants were transgender
  - 21 provided information on race and ethnicity of participants
  - 16 provided information on number of participants older than 50

# Demographics of current enrollment

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Category (N=respondents)	#/total	%	Mean	Median
Total participants (N=60)	2754	---	45	12
Female participants-sex (N=31)	260/1549	16.7%	8	1
Women participants-gender (N=20)	230/1241	18.5%	11	1
Transgender (N=20)	18/1233	1.4%	1	0
Participants over 50 (N=16)	49/731	6.7%	3	2

# Demographics of current enrollment

Category (N=respondents)	#/total	%
White participants (N=21)	117/843	13.9%
Black participants (N=21)	71/843	8.4%
Asian participants (N=21)*	629/843	74.6%
Hispanic participants (N=21)	26/843	3.1%
White participants (N=20)**	117/219	53.4%
Black participants (N=20)**	71/219	32.4%
Asian participants (N=20)**	12/219	5.5%
Hispanic participants (N=20)**	26/219	11.9%

\*617 of the 629 Asian participants are enrolled in a Thai study

\*\* Data excluding that Thai study

Next steps

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# Information Dissemination

- Results submitted to Journal of Virus Eradication
- Community write-up will be shared after publication
- Focus groups/panel discussion with researchers and community advocates addressing some of these topics

# Additional data gathering

- Follow-up interviews with survey respondents
  - Community outreach – how are plans determined and monitored?
  - Data sharing: enthusiasm levels, logistics
  - Reasons for not setting formal or informal demographic targets
  - Partner PrEP provision in ATI trials
  - Compensation decisions
- Interviews with community advocates to develop recommendations and guidance for funders and for advocates

**THANK YOU**

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