



Summaries of articles in: *Critical Comorbidities in the Modern Antiretroviral Era: Baseline Demographic, Metabolic, and Immune Characteristics of the Global REPRIEVE Trial Population. Journal of Infectious Diseases, Volume 222, Issue Supplement 1 August 2020*

Leveraging a Landmark Trial of Primary Cardiovascular Disease Prevention in Human Immunodeficiency Virus

Introduction From the REPRIEVE Coprincipal Investigators, Steven Grinspoon, Pamela Douglas, Heather Ribaud, and Udo Hoffmann

The health impact and prevalence of heart disease and other medical conditions, also known as comorbidities, on an aging global population with human immunodeficiency virus (HIV) are described in this collection of articles in *The Journal of Infectious Diseases*.

This collection contains the first set of important data from the world's largest study of heart-related disease prevention in people with HIV, known as **Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)**.

From 2015 to 2019, REPRIEVE enrolled 7,770 participants from over 100 clinical sites across 5 continents. The participants represent a diverse group of individuals living with HIV by race, ethnicity, and gender.

The participants:

- › Ages of 40-75 years
- › On antiretroviral therapy
- › Had low-to-moderate heart disease risk

The purpose of REPRIEVE is to test if Pitavastatin Calcium, a statin medication and referred to as pitavastatin, reduces the risk of heart disease-

including heart attack and stroke-among people with HIV. The study also looked at participant characteristics and comorbidities including:

- › Antiretroviral therapy use and immune profiles
- › Reproductive aging transitions in women (menopause)
- › Gender identity, waist measurement, and metabolic disease
- › Baseline kidney function
- › Impaired physical function and frailty
- › Antiretroviral therapy use and myocardial steatosis (build-up of fat in the heart muscle cells)

The summaries below provide detailed descriptions of each article included in the *Journal of Infectious Diseases* supplement. The full text articles can be found [here](#).



The findings shared in these summaries are from the REPRIEVE population at a specific point in time, these findings are descriptive and not intended to change clinical care, if you have questions about what you've read please talk to members of the REPRIEVE study team at your local site or a health care provider.

Patterns of Antiretroviral Therapy Use and Immunologic Profiles at Enrollment in the REPRIEVE Trial

Carl Fichtenbaum, Steven Grinspoon and colleagues



Currently, the availability of antiretroviral therapy and how antiretroviral therapy is prescribed has seen major shifts across the globe. REPRIEVE is an opportunity to explore these patterns.

Investigators of REPRIEVE looked at:

- › Patterns of antiretroviral therapy use between 2015 and 2019
- › Patterns of antiretroviral therapy use and the immune system, including CD4 count (a white blood cell that fights infection) and CD4:CD8 ratio (a ratio of two different white blood cells and a measure of immune function)
- › Measures of immune function relating to key participant characteristics such as body composition

The participants:

- › 7,770 participants total
- › Average age: 50 years
- › 31% were natal female (female at birth)
- › 43% were Black or African American

The investigators found that there were differences in antiretroviral therapy use by geographic region, as well as changes in antiretroviral therapy use over the four-year enrollment period.

The different patterns reflect:

- › Local availability of specific antiretroviral therapy medications
- › Changes in treatment guidelines
- › Provider and patient preferences in antiretroviral therapy

Investigators looked over key markers of the immune system, like the number of CD4 cells and the ratio of CD4 cells to CD8 cells, of REPRIEVE participants, and found that across all regions, higher CD4 counts were associated with:

- › Being female
- › Longer antiretroviral therapy use
- › Higher body mass index

Similarly, higher CD4:CD8 ratio was associated with:

- › Being female
- › Longer antiretroviral therapy use
- › Higher nadir CD4 count (nadir CD4 is a person's lowest CD4 count known)

These findings will help guide future studies on antiretroviral therapy and the immune system as well as other characteristics such as body mass index in other global studies among people with HIV.



Correlates and Timing of Reproductive Aging Transitions in a Global Cohort of Midlife Women with Human Immunodeficiency Virus: Insights From the REPRIEVE Trial

Markella Zanni, Sara Looby and colleagues

Previous studies have shown that more advanced reproductive aging (transition through and past menopause) relates to the risk of heart disease. However, less is known about reproductive aging among women with HIV. REPRIEVE presents a unique opportunity to learn more about reproductive aging among women with HIV across the globe.

In this study, the investigators examined the reproductive aging process among cisgender female participants (female participants whose gender identity matches their sex at birth) with HIV and the possible timing of the transition to menopause.

This was looked at based on two factors:

1. Menstrual history
2. Levels of a reproductive aging hormone called antimullerian hormone (lower levels of this hormone reflect increased reproductive aging)

The participants:

- > 1,449 cisgender women total
- > 45-55 years old
- > 63% Black or African American
- > 18% Asian

Results showed that women with HIV living in certain regions (including sub-Saharan Africa and Latin America and the Caribbean) and women with higher waist measurement had greater odds of having more advanced reproductive age. Age of menopause was typically in the age range of 49 to 51.

When REPRIEVE is completed, we will be able to look at how reproductive age relates to the risk of heart disease among women with HIV.



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Characteristics of REPRIEVE Trial Participants Identifying Across the Transgender Spectrum

Laura Smeaton, Karin Klingman and colleagues



Persons identifying across the transgender spectrum (PATS) are at higher risk for getting HIV, but are often represented in numbers that are inaccurately low in research and clinical studies. REPRIEVE is one of the first studies to look at gender identity among the participants.

Gender identity is how a person feels and who they know themselves to be when it comes to their gender. Gender identities may include terms like cisgender, transgender, gender queer, gender non-conforming, or gender variant.

With terms like trans-feminine, transgender female, and trans male, it is sometimes unclear whether people whose identity is not trans (for example, genderqueer or gender non-conforming) are included or not. For this reason, it is important to lower information gaps by using consistent terms that capture everyone.

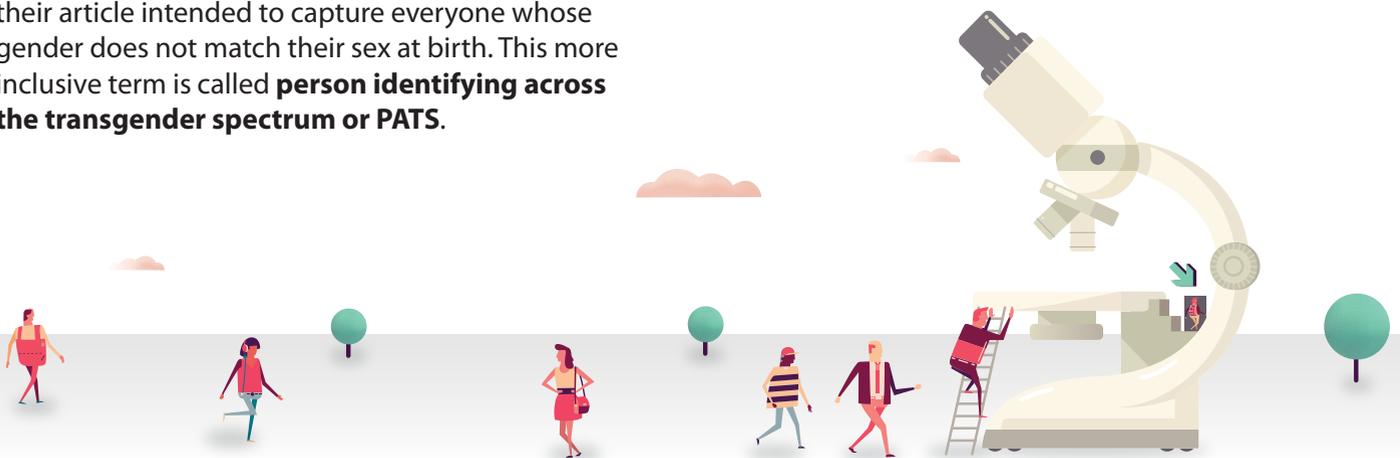
Among REPRIEVE participants, the investigators found that 30% (or 3 out of 10) of non-cisgender males (gender identity differs from male sex) did not identify as transgender. As a result, they were not captured by terms like transgender female. Because of this, the investigators presented a new term in their article intended to capture everyone whose gender does not match their sex at birth. This more inclusive term is called **person identifying across the transgender spectrum or PATS**.

When looking at the PATS population in REPRIEVE:

- > 0.3% of natal females (female at birth) identified as PATS
- > 2.4% of natal males (male at birth) identified as PATS

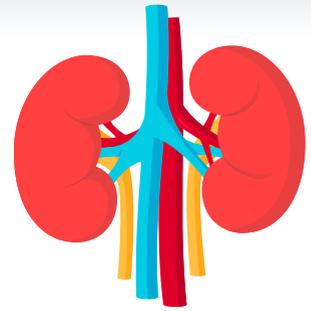
Among natal males, the investigators found that PATS tend to have a higher waist measurement (greater than 102 centimeters or about 40 inches) than cisgender males. A higher waist measurement may put PATS at higher risk for metabolic disease such as heart disease or diabetes mellitus.

The take home message is that consistently reporting gender identity will fill knowledge gaps needed to prevent and treat illness among people with HIV who identify across the transgender spectrum.



An Evaluation of Baseline Kidney Function in the REPRIEVE Trial

Turner Overton, Christina Wyatt and colleagues



Chronic kidney disease is a recognized medical condition among people living with HIV. Common risk factors of chronic kidney disease include race, diabetes mellitus, and high blood pressure. Among people with HIV, inflammation may also increase risk of chronic kidney disease. Previous studies have shown that statin medications, including pitavastatin, improve kidney function in people without HIV. Thus, pitavastatin may also have a beneficial effect on kidney function in REPRIEVE participants.

The participants:

- > 7,770 participants total
- > Average age: 50 years
- > 31% female
- > 43% Black or African American

The investigators looked at differences between 3 equations that are commonly used to estimate glomerular filtration rate, a measure kidney function, by race and region of enrollment in REPRIEVE.

The 3 equations were:

1. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimation of glomerular filtration rate
2. Modification of Diet in Renal Disease (MDRD) estimation of glomerular filtration rate
3. Cockcroft-Gault Creatinine Clearance equation

The key findings were:

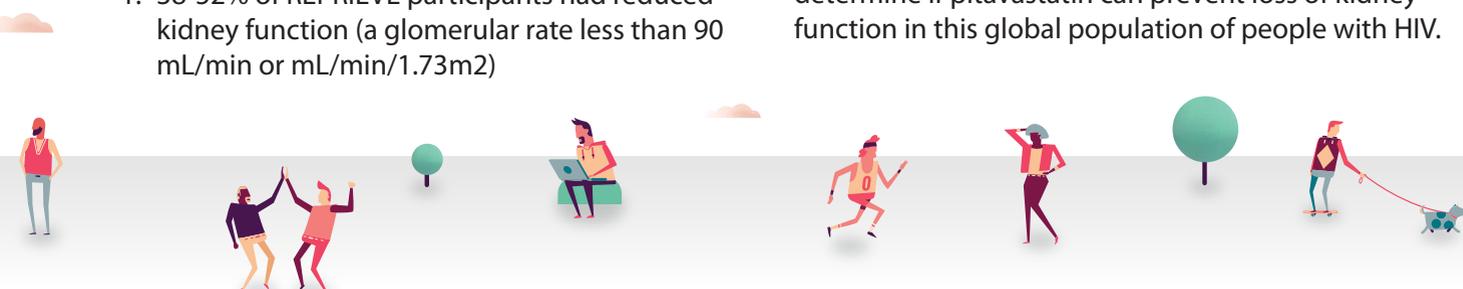
1. 38-52% of REPRIEVE participants had reduced kidney function (a glomerular rate less than 90 mL/min or mL/min/1.73m²)

2. Kidney function tended to be lower in higher income regions (for example, North America):
 - > 53% of REPRIEVE participants from higher income regions had low kidney function
 - > 26% of participants from other regions had low kidney function.

The investigators also found that certain risk factors for kidney disease were associated with higher odds of reduced kidney function, including:

- > Older age
- > Higher body mass index
- > History of high blood pressure
- > History of chronic viral hepatitis
- > Exposure to tenofovir-based antiretroviral therapy

The data collected in REPRIEVE will allow future research on changes in kidney function over the follow-up period. The ultimate goal will be to determine if pitavastatin can prevent loss of kidney function in this global population of people with HIV.



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Physical Function Impairment and Frailty in Middle-Aged People Living with Human Immunodeficiency Virus in the REPRIEVE Trial Ancillary Study PREPARE

Triin Umbleja, Kristine Erlandson and colleagues



Physical activity and body mass index are important factors that people can change. These factors may help older people with HIV prevent a decline in physical function. Investigators determined this from 266 participants, from the Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE) study.

PREPARE is a smaller study within REPRIEVE. The purpose of PREPARE is to evaluate the impact of pitavastatin on muscle and physical function among middle-aged adults participating in REPRIEVE.

The participants:

- > 266 participants total
- > 81% were natal male (male sex at birth)
- > 45% Black or African American
- > 18% Hispanic

The investigators found that:

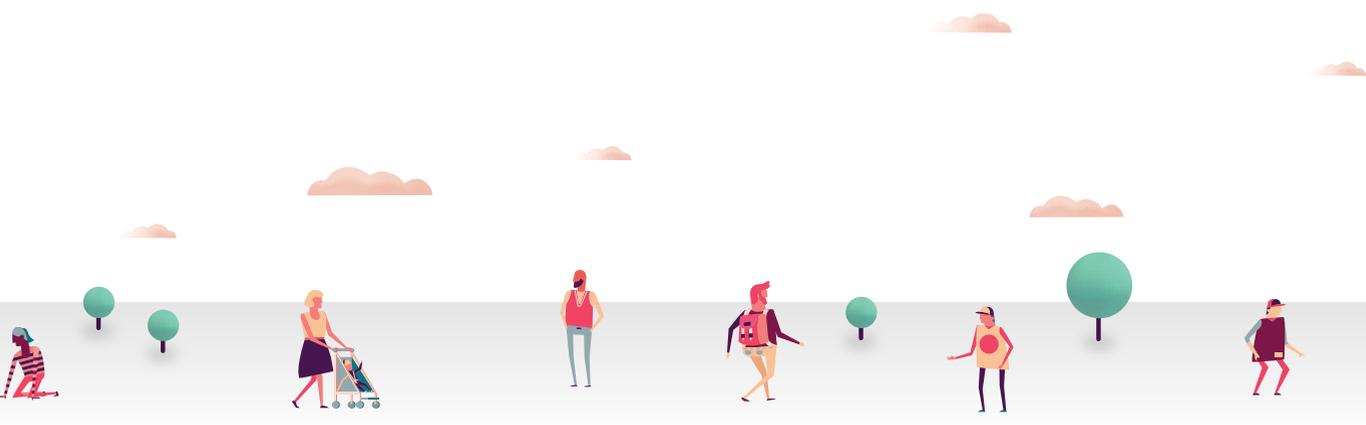
- > 37% of participants had impairments in physical function measured by a short physical performance test
- > 6% were frail
- > 42% pre-frail

- > 31% reported not being able to perform one or more important activities of daily living such as eating, dressing, work around the house.

The investigators found that physical function impairment was associated with:

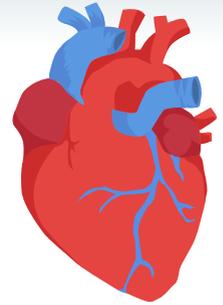
- > Older age
- > Black or African American race
- > Higher body mass index
- > Physical inactivity

In summary, the investigators found that physical function impairment was common among middle-aged people with HIV. Moreover, changing physical activity and body mass index may be helpful to maintain physical function.



Myocardial Steatosis Among Antiretroviral Therapy-Treated People with Human Immunodeficiency Virus Participating in the REPRIEVE Trial

Thomas Neilan, Markella Zanni and colleagues



The REPRIEVE study allows investigators to gather and analyze data relating to heart health among people with HIV on antiretroviral therapy. Previous studies have shown that people living with HIV face a higher risk for heart failure. Heart failure is a condition in which the heart is unable to pump enough oxygen-carrying blood to meet the body's needs. Heart failure can be caused by build-up of fat in the heart muscle cells, also known as myocardial steatosis.

The purpose of this study was to look at possible risk factors for myocardial steatosis among people with HIV on antiretroviral therapy. This is a smaller study within REPRIEVE.

The participants:

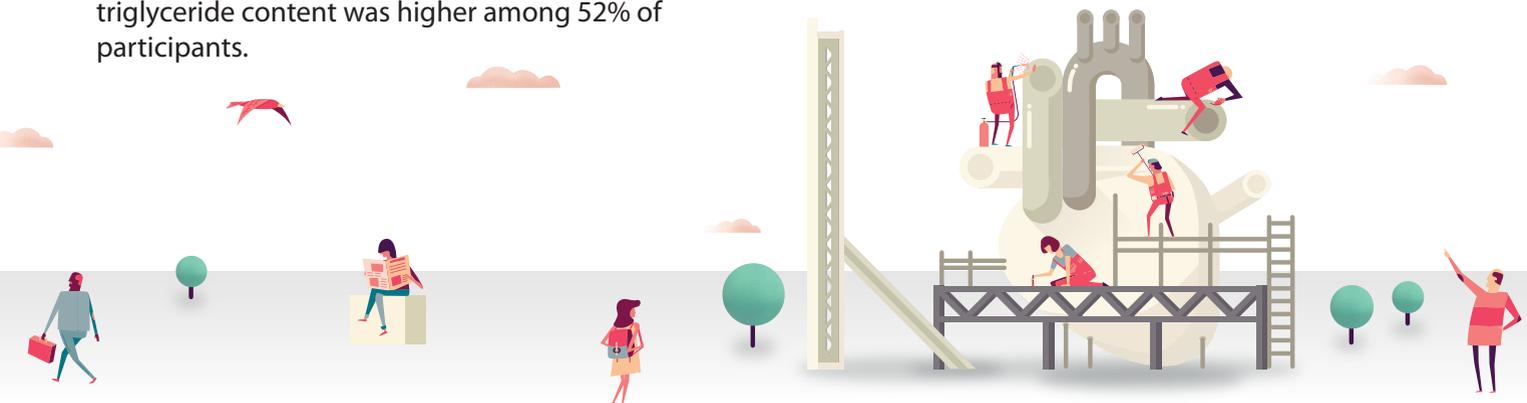
- > 82 participants total
- > 88% were natal male (male sex at birth)
- > 41% Black or African American
- > 28% Hispanic

All participants underwent cardiac magnetic resonance spectroscopy, a noninvasive imaging test that measures fat in the heart muscle cells. The result was given in intramyocardial triglyceride (IMTG) content. The higher the intramyocardial triglyceride content, the more fat build-up in the heart muscle cells. Results showed that intramyocardial triglyceride content was higher among 52% of participants.

The investigators found that higher intramyocardial triglyceride content was associated with:

- > Older age
- > History of intravenous drug use
- > Lower nadir CD4 count (nadir CD4 is a person's known lowest total CD4 count)
- > Body mass index of 25 kg/m² or higher (being overweight or obese)

A better understanding of risk factors related to myocardial steatosis among people with HIV will help us develop strategies to prevent fat build-up in the heart muscle cells. The ultimate goal of this work would be to find ways to lower the risk of heart failure among people with HIV.



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References

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