

VOICE Trial: Behavioral challenges in preventing HIV

Justin Greene | Monday | December 2, 2013

Outline

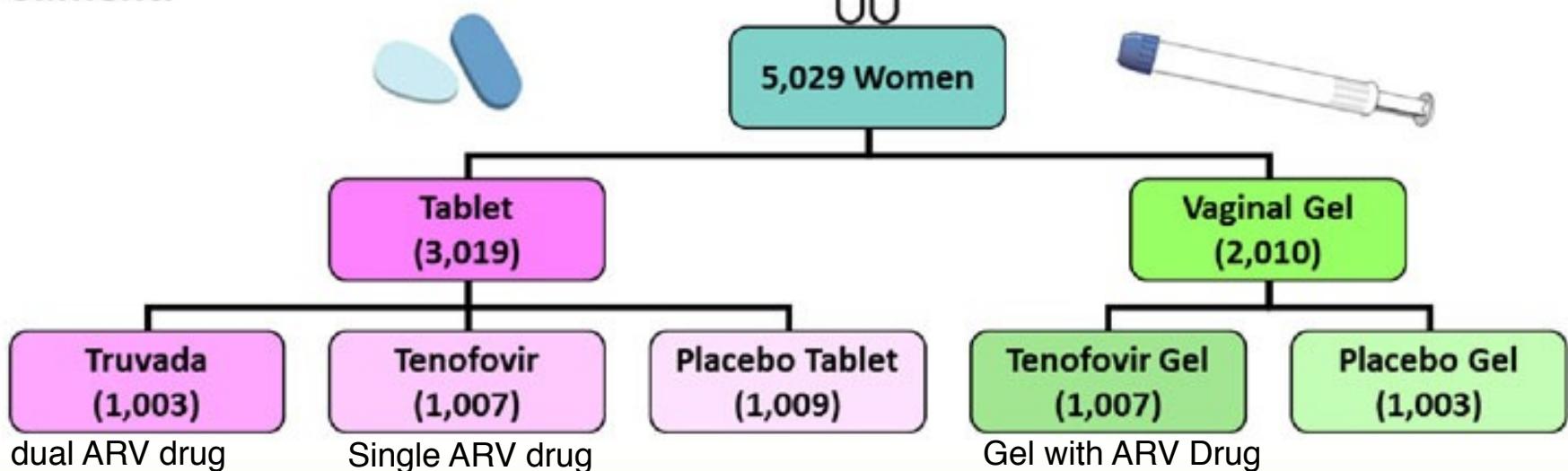
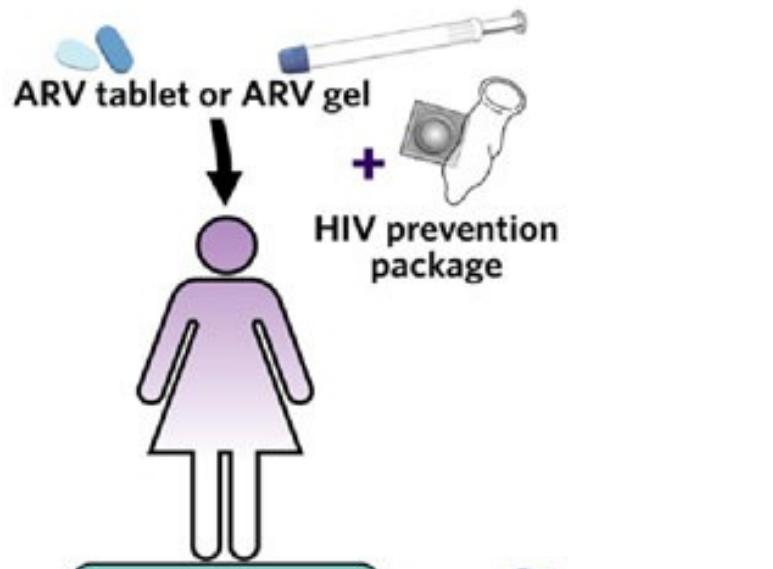
- The VOICE (MTN-003) trial in detail
 - What happens in a clinical trial?
 - What do we measure?
 - What are people doing to address issues/challenges?
- The social and structural factors that impact HIV transmission today



Voice trial was testing PrEP: Pre-exposure prophylaxis

Vaginal + Oral Interventions to Control the Epidemic

VOICE enrolled 5,029 women, but the final analysis of study data is based on **5,007 participants**; **22 women were not included** because they were later identified to have been infected at the time of enrollment.



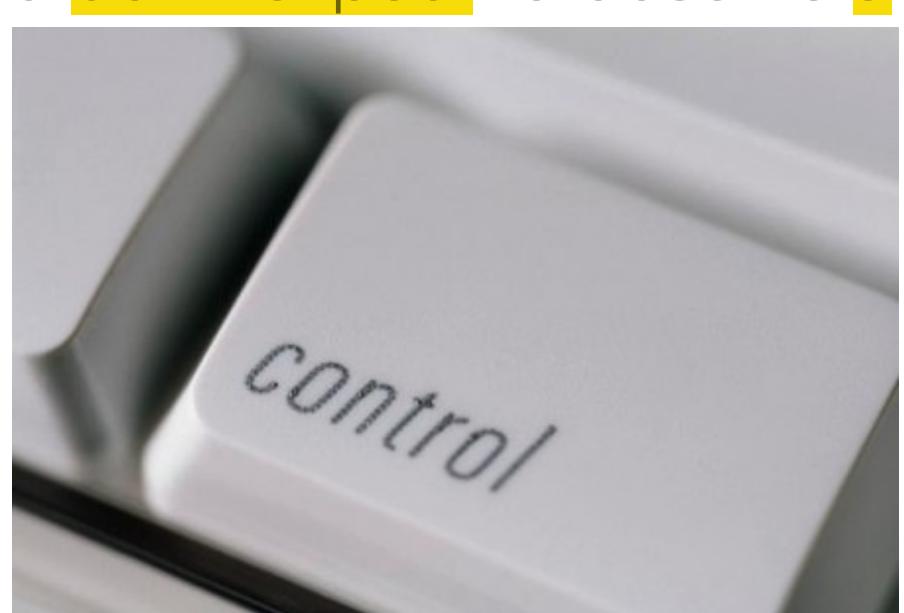
What are placebos?

- Placebos appear similar to a medication being tested in a trial
- Placebos provide an important **negative control**
- Controls ensure that the **results** you observe in clinical trail or experiment **are due to the intervention** you are testing
- **Both** clinicians and participants were **blinded**

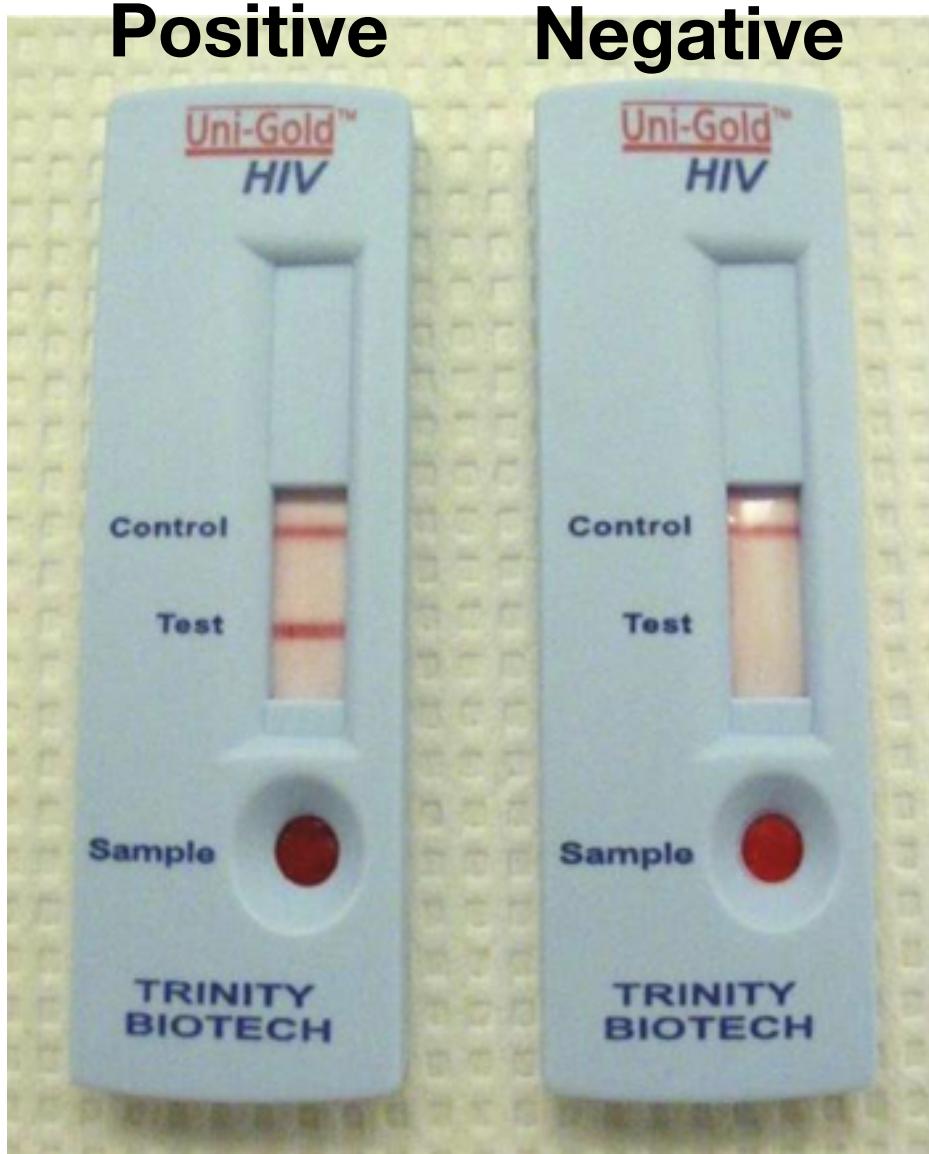


Experimental Controls

- Experimental controls are critical to ensuring that confounding variables are not responsible for your results
- Positive control is where you expect to observe a result
- Negative control is where you don't expect to observe a result

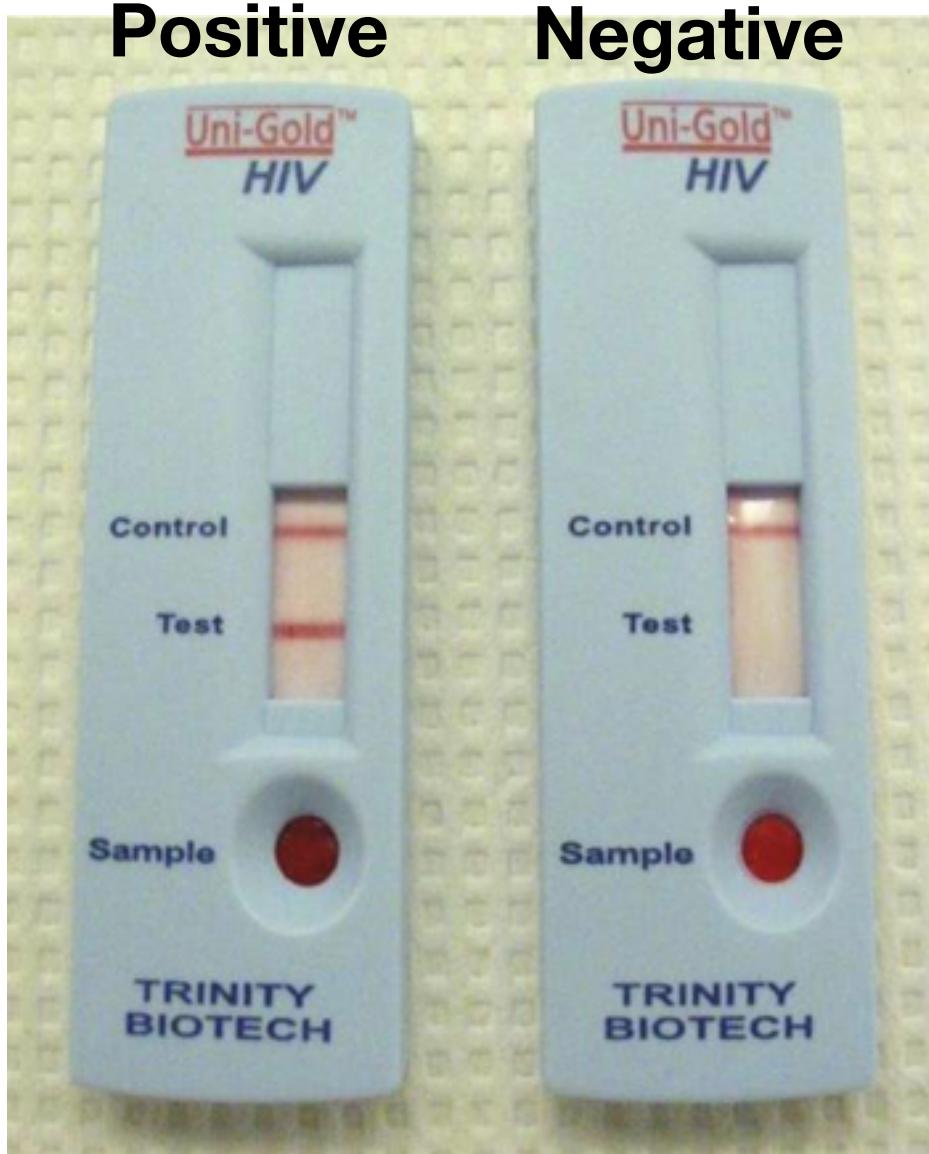


Positive control example - why does HIV test have control?



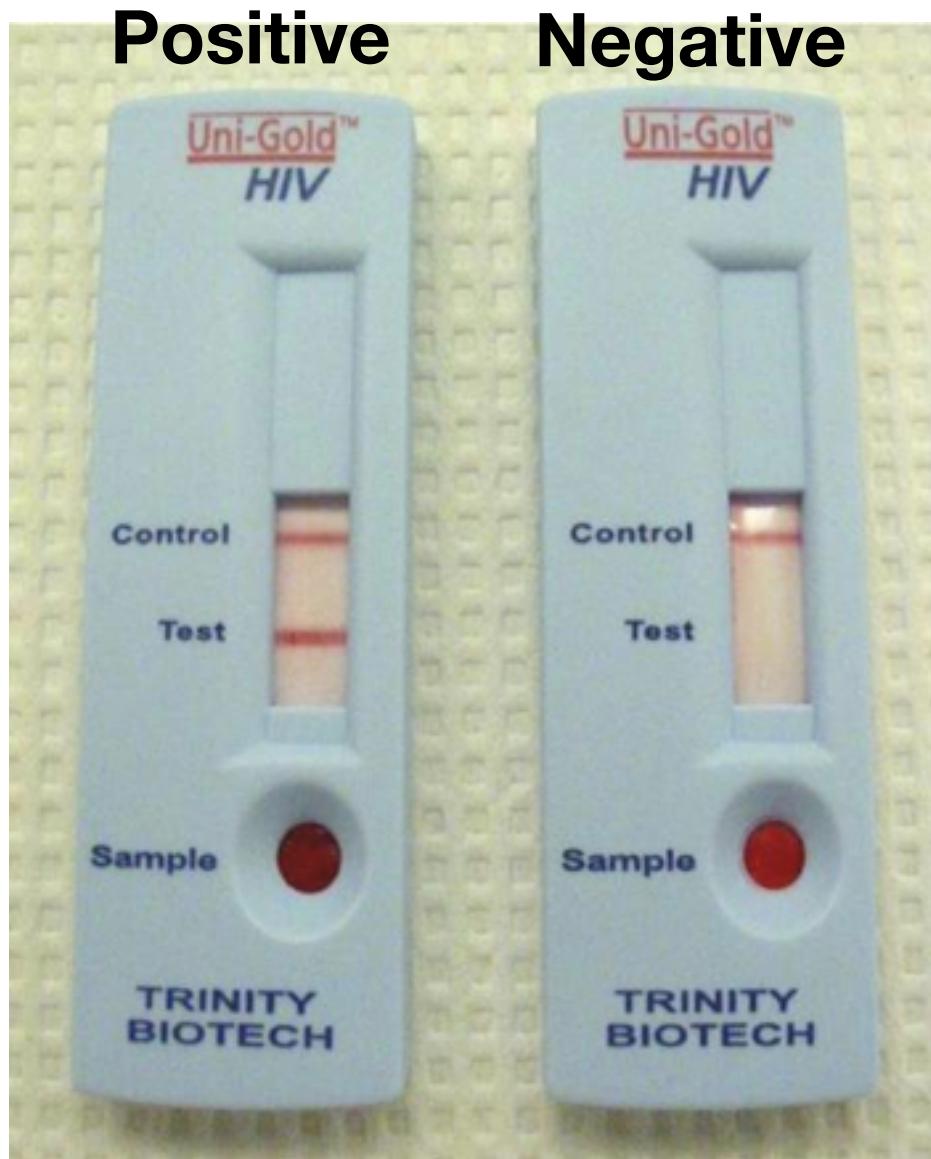
- HIV test has positive control band to make sure the test worked
- This band should appear positive whether person being tested has HIV or does not have HIV

Positive control example - why does HIV test have control?



- HIV test has positive control band
- This band should appear positive whether person being tested has HIV or does not have HIV
- The control ensures the test is working properly

Negative controls and HIV tests



- New batches of an HIV test are screened with blood known to be HIV negative.
- Ideally, ensures that the tests yield positive result only when expected

Key Terms in discussion experimental controls

- False negative - negative result when a test should be positive
 - HIV+ individual has a negative result

happens in early stages of infection because antibodies have not developed
often told to wait or use different tests
- False positive - positive result when a test should be negative
 - HIV- individual getting a positive test result

tests may be designed to give more false positives so you're catching everyone w/ HIV
antibodies that cross react w/ HIV; every positive is followed by a second test

People often take glucosamine for joint pain due to loss in cartilage. You would like to test whether glucosamine leads to a reduction in joint pain and whether it actually restores cartilage.

What experimental groups should we use to test this? What should we measure? How?



Experimental Groups

- People with joint pain - we explain we are testing glucosamine
 - Group 1: Glucosamine
 - Group 2: Placebo

placebo effect: people may think that they are taking glucosamine and say that joint pain has gone away but really hasn't
- People with joint pain - explain we are testing something else (maybe a multivitamin for cardiovascular disease?)
 - Group 1: Glucosamine
 - Group 2: Placebo

unethical since people don't know what they are taking

Measurements

- Self-assessments of joint pain
- Ability to perform a task - walk one mile
- Actual measurements of cartilage by x-ray?

Voice Trial Endpoints

- Effectiveness measured by seroconversion -becoming HIV+
- Safety -of the drugs on a daily basis
- Explore adherence, HIV drug-resistance, and drug concentrations vs. effectiveness

people with more amounts of the drugs, we can expect to be less likely to get the disease
-it's still important to measure

Beyond MTN-003

sub-studies:



- MTN-003B: Bone Mineral Density Substudy
- MTN-003C: The Community and Adherence Substudy
 - outside forces that effect adherence
- MTN-003D: Understand woman's actual use and sexual behaviors
 - Why did women remain in the trial when so few adhered to the product

First need to recruit trial participants

- Sites
 - Uganda, Zimbabwe, and South Africa
 - “Encompassing a region where HIV incidence is highest in the world”
 - Why here?

Need to determine appropriate site for multiple reasons

- Need the health care infrastructure to perform the study
- Need to identify willing trial participants need to track and such
- Known risk of contracting HIV

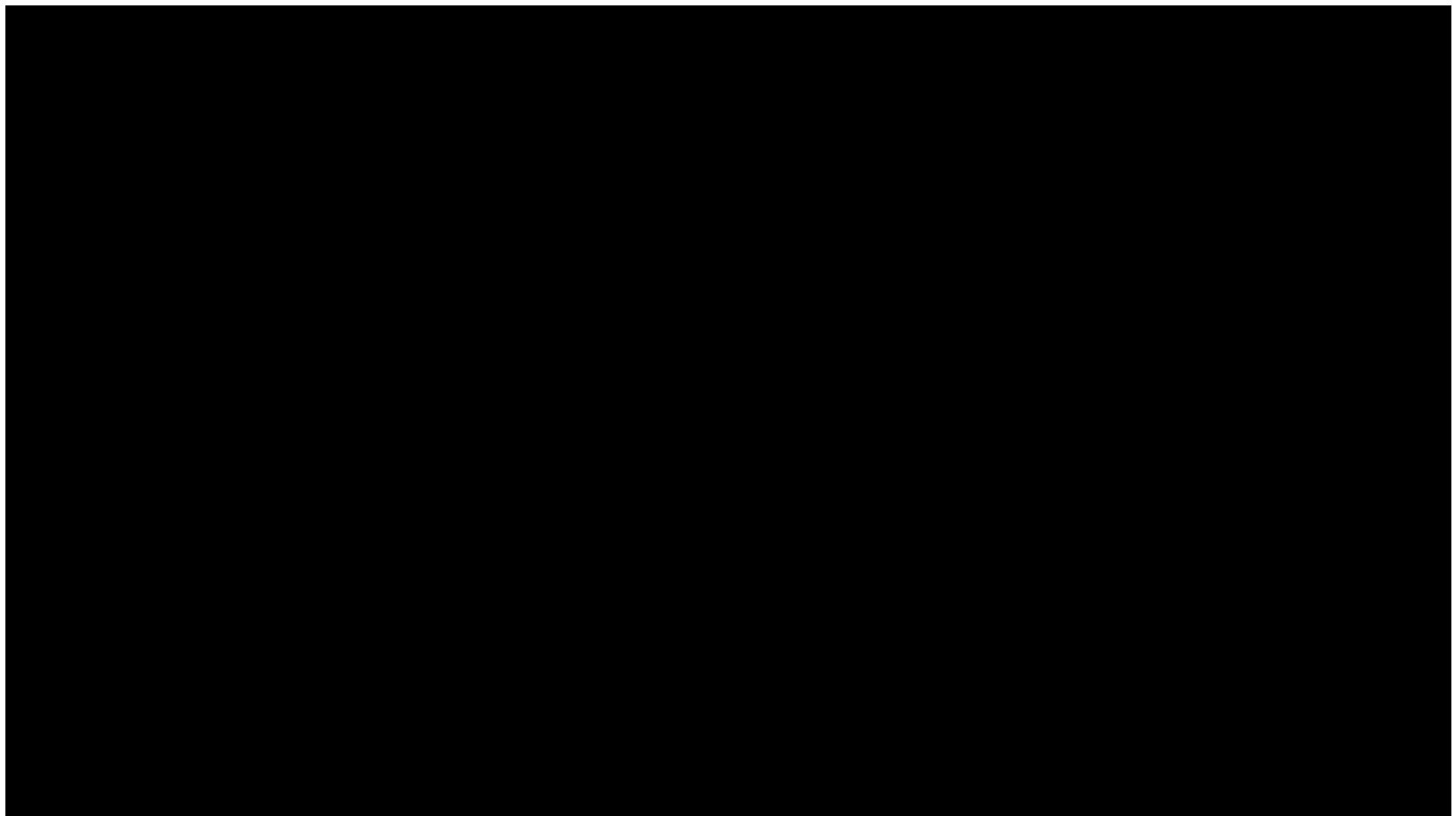


Harare Zimbabwe - Seke South Clinical Research Site Team

Advertising a trial



Advertising in the United States



Screening People for a Trial

- Enroll desired participants
 - HIV negative Women - 18-45 years
 - Avg: 25.3 and 79% were single
 - Not pregnant and using contraception
 - Not enrolled in other clinical trials
 - Can provide informed consent

Randomized



- People are distributed between groups randomly to ensure results are not due to a particular grouping
- Example - You are testing whether a vaccine can protect people against HIV
 - One might unconsciously make a group of people who are at lower risk for contracting HIV
 - Problem - One group may randomly be enriched for specific attributes like age/sex/etc.

Monitoring subjects during the trial

- Participants should have visit the clinic every 28 days after enrollment
- Follow-up includes:
 - Counseling on HIV prevention and condom distribution
 - HIV and STI testing if they are positive they need to be able to get those people into care
 - Adherence counseling

PTID:	Visit Date:
<p><input type="checkbox"/> 1. Insert one applicator or take one lighter tablet and one darker tablet every day.</p> <ul style="list-style-type: none">• As close as possible to the same time every day• Even on days when you do not have sex• Even on days during menses <p><i>How might you plan to do this? At what time do you think you will insert gel or take tablets each day? Is there an activity you do every day that might help you to remember to insert gel or take tablets every day?</i></p> <p><i>If assigned to gel: You might find that some gel leaks out after insertion. This is normal. Because of this, you may want to use panty liners which we can give you. You also may want to consider inserting gel at bedtime. You should also consider when you and your partner usually have sex, as this could help determine when you would like to insert gel (explore advantages and disadvantages).</i></p> <hr/> <hr/> <hr/> <hr/> <hr/>	

- 2. If you miss a dose, insert gel or take tablets as soon as you remember, but skip the missed dose if your next dose is due within 6 hours.**

Example: Let's say you usually take your dose at about 6:00 pm (around dinner time). If you forget to take a dose, and realize this when you wake up at about 6:00 am the next day, you should take the missed dose immediately, because there are about 12 hours left before the time of your next dose. On the other hand, if you did not realize that you missed a dose until your children come home from school, at about 3:00 pm, you should skip the missed dose, because there are only about 3 hours left before the time of your next dose.

Follow-up Adherence Counseling Worksheet

PTID:

Visit Code:

1. WELCOME: Greet and thank participant and establish rapport.

2. FRAME: Explain the purpose of discussion and seek permission.

3. EXPLORE: The context (experiences) in which the participant feels it is easiest and hardest to use the study product. Check in on how things went with the goals set at the last session; reinforce efforts and move on to exploring ease and difficulty now.

CONTEXT (EXPERIENCES)

... made it feel easier...

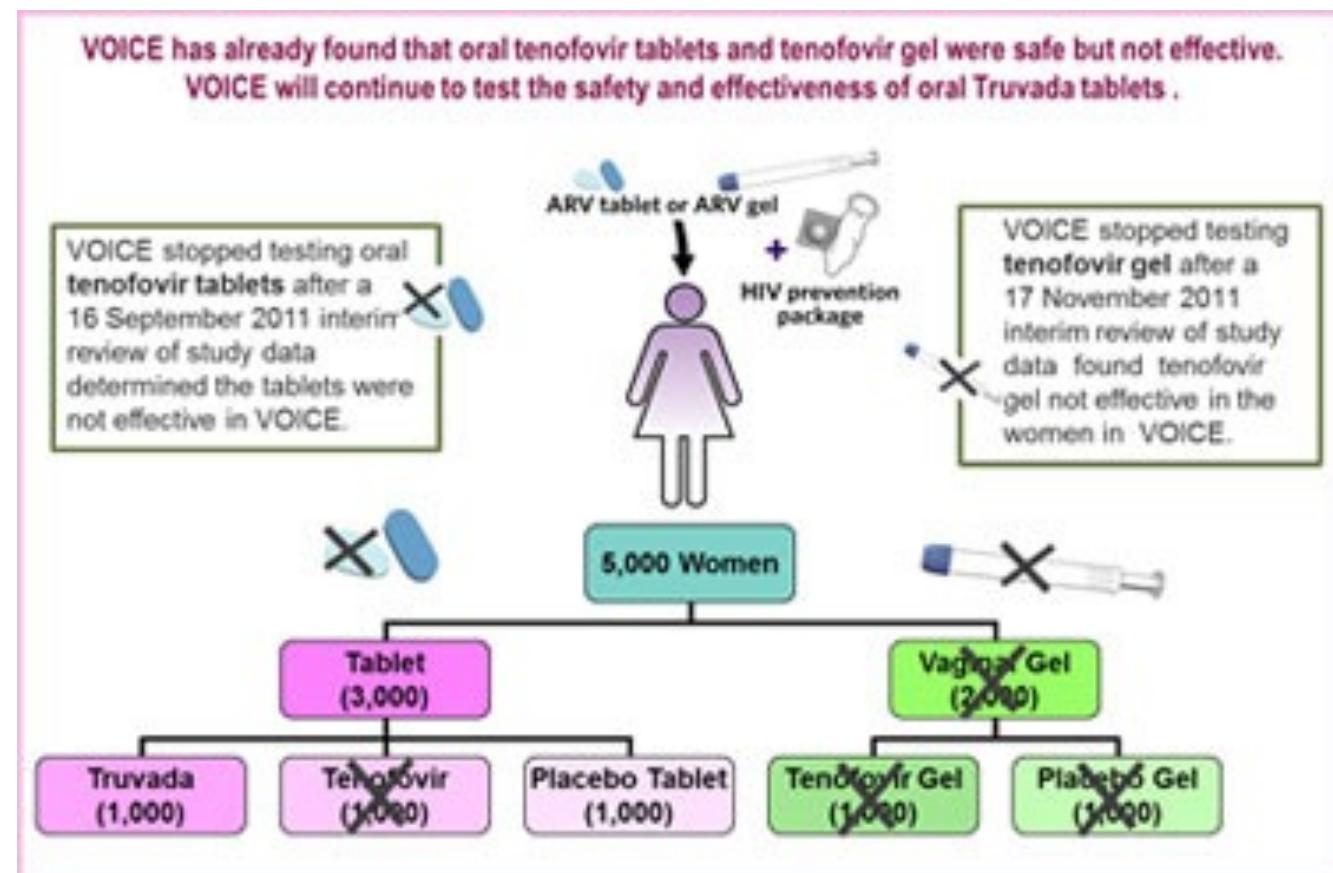
... made it seem difficult ...

CONTEXT AROUND EXPERIENCES WITH PRODUCT: REGARDLESS OF ACTUAL PRODUCT USE

****Please show participant what you are writing if you write notes during the session****

Evaluating trial results

- A data safety and monitoring board evaluates interim results to ensure participants not adversely affected
- Met approximately every 6 months



not blinded to who has the placebo

VOICE Trial Results

Compared to its matched placebo, no product was effective in VOICE

61 infections



60 infections



52 infections



35 infections



61 infections



70 infections



Truvada



Placebo

The number of HIV infections in the Truvada and oral placebo groups were compared at the end of the study

The number of HIV infections in the oral tenofovir and oral placebo groups were compared on the date sites began telling participants the tenofovir arm was closing (Oct. 3, 2011)

Placebo



Tenofovir Gel



Placebo Gel

The number of HIV infections in the tenofovir gel and placebo groups were compared at the end of the study

Adherence

- Drug was detected in less than 30% of women in trial
despite apparent and reported adherence of 90%
- HIV incidence for young unmarried women reached >8% while 0.8% in older married women
- Adherence was lowest in young women
adherence was lowest was in single women who are young

Why do we measure adherence?

Why do we measure adherence?

- We cannot assess the efficacy of a given intervention if we do not know whether it was actually used
- We can identify patterns regarding efficacy and use with this information
- We do not know whether people are likely to use a product unless we ask

goal: find a product that people are willing, able and want to use

Not the women's fault

How will researchers determine why adherence was low in the VOICE Trial?

Beyond MTN-003

- MTN-003C: The Community and Adherence Substudy
 - Assess external community factors that might contribute to or detract from adherence
 - Participants:
 - 102 VOICE Trial participants
 - 26 male partners
 - 23 community stakeholders (HIV activists, church leaders, journalists, government officials etc.)

Beyond MTN-003

- MTN-003D: Understand women's actual use and sexual behaviors
 - In depth interviews with participants to understand their beliefs and attitudes about HIV risk
 - 200-250 former trial participants

Sample MTN-003D Interview Questions

- Can you tell me all the reasons that you joined VOICE
- Before you joined VOICE, how worried were you about getting HIV or having HIV?
- Think about what life is like for women here in [relevant country]. Please describe the aspects about this place or this society that might have made it difficult for women to use [tablets/gel] every day during VOICE.

Potential reasons for non-adherence (speculation!)

in terms of the VOICE trial

- Forgetting
- Depression, anxiety, substance abuse problems
- Side effects
- Negative attitudes about HIV
- Lack of understanding of benefits
- Lack of social support

What happens to people after the trial ends?

- People who test HIV positive are counseled and pointed towards appropriate treatment meets or exceeds community standards
- MTN-015
 - recommended for participation in this trial
 - Trial follows those who seroconvert while on trial
 - Why is this important?



MTN-015

- Do people who seroconvert do better than those infected outside of a trial?
- Are they more likely to develop drug resistant HIV?
- Do people who are infected during a trial progress more rapidly?
- How do participants respond to treatment?

Reasons some women do not pursue treatment after seroconversion in a trial

- Fear of disclosure to family/friends
- Stigma and discrimination (knowing people who work at the clinics)
- Concerns about ARV side-effects
- Work commitments
- Cost and distance
- Traditional Medicines
- Still feel healthy



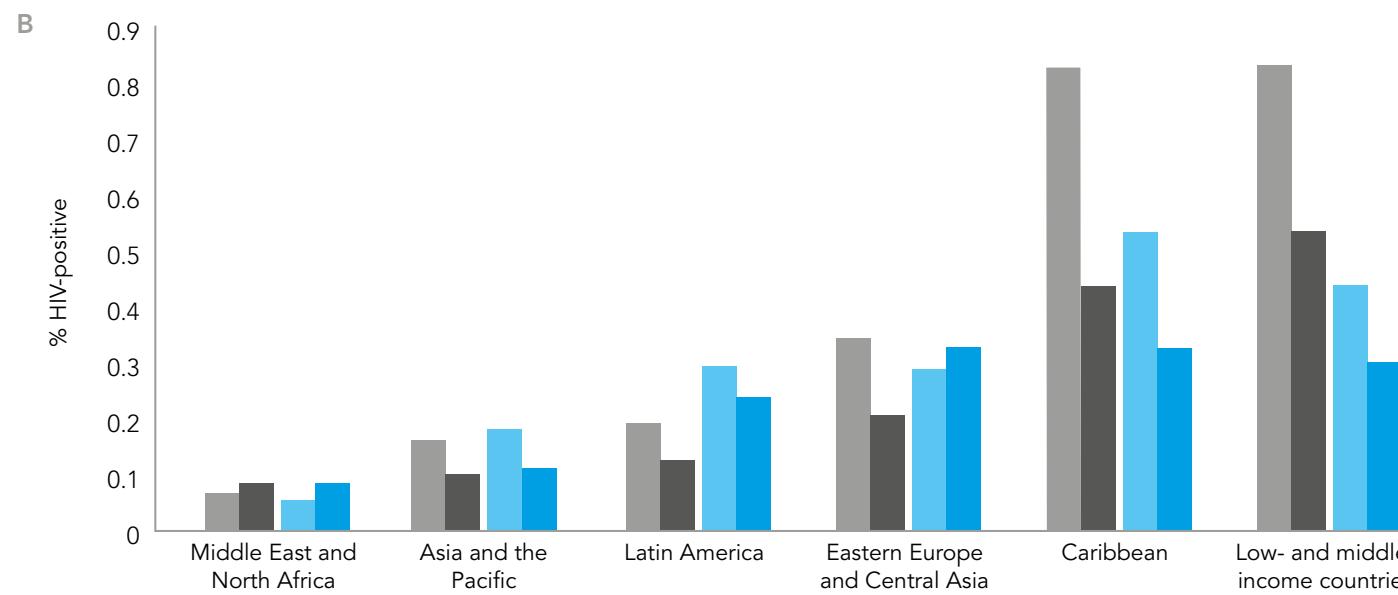
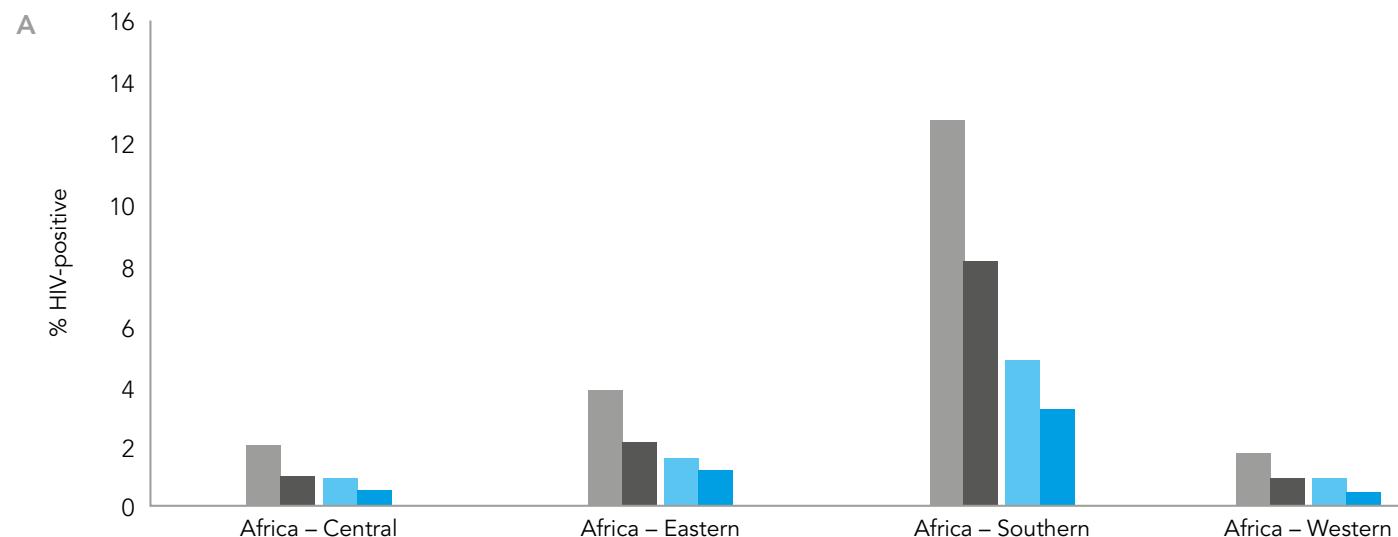
Voice Summary

- No interventions were able to reduce the incidence of HIV
- Trial participants did not utilize the oral tablets or vaginal gels in this trial
- Ongoing studies will seek to determine why women did not adhere to the products tested in this study
- Work continues on products that may be more compelling and lead to better adherence

Why was the voice trial
interested in empowering women
to protect themselves?

Prevalence of HIV among young women and men (15–24 years), by region, 2001 and 2012

Women in sub-saharan Africa are more likely to have HIV



■ Women 2001

■ Women 2012

■ Men 2001

■ Men 2012

The countries of Sub-Saharan Africa were formerly colonies of European countries.

How did colonial economies affect women?

Colonialism and economy

- Before European conquest, women played key role in traditional economic systems.
- Masai women bartered livestock for other goods.
- British government replaced informal economy with a cash economy controlled by men.
- Easier to monitor and tax.



Colonialism and economy

- In South Africa, Europeans took over fertile land and settled people in “homelands” and townships.
- Men encouraged to work in extractive industries like mining.
- Men were separated from their families for long periods of time.



More likely to engage with CSW

Gender inequality contributes to the spread of HIV.

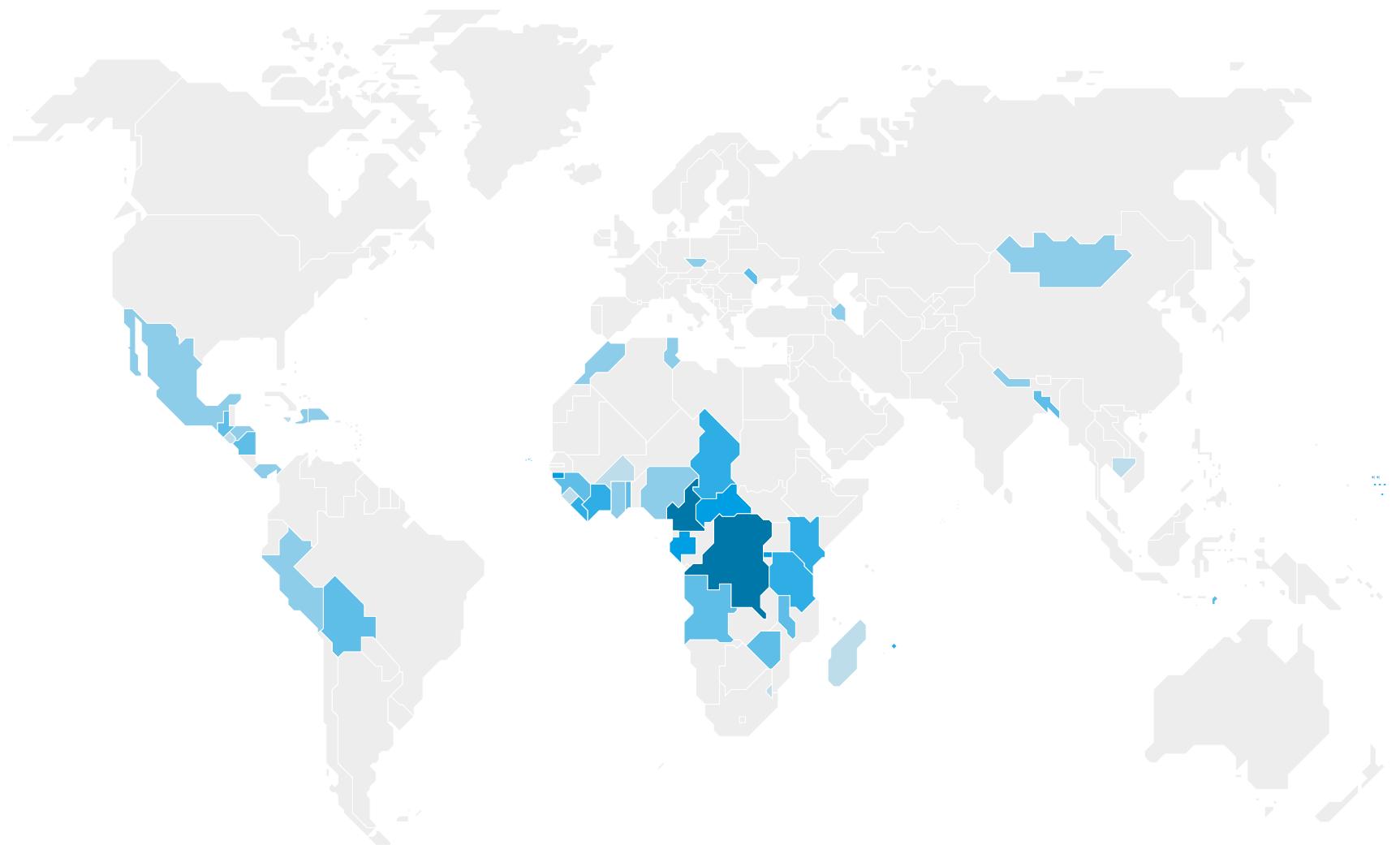
- Changes in **economic status**: colonialization, globalization; uncertainty about employment
- **Transactional relationships** raise risk of HIV infection
 - these go on for a long period of time rather than CSW (sugar daddy)
- Gender-based **violence**, inequality increase risk of HIV infection

“Asymmetries” in relationships

- Economic: “A man’s beauty is considered by his wealth.”
- Age: Young women frequently seek transactional relationships with older men. Older men have more exposure to women (a larger opportunity window to contract HIV)
- Power: Can negotiate formation and continuation, but not much else. Violence, coerced sex.

Women can negotiate when to start a transactional relationship and stay in one but not much else

Intimate partner violence in the past 12 months reported by women aged 15–49 years



5–10% 10–20% 20–30% 30–40% 40–50% 50–69% No data available

Women who have experienced intimate partner violence were
50% more likely to acquire HIV

Possible motives for sexual violence in contemporary Sub-Saharan Africa

- Rape is likely an assertion of power, not sexuality.
- Women are increasingly entering roles that are traditionally male.
- Studies suggest that independent women are frequent targets: exertion of control.
- Men in transactional relationships feel that sex is part of the “implicit sexual contract.” Sex is owed to the man

Concepts to understand

- AIDS in Sub-Saharan Africa exists in a “social ecology.” It’s closely tied to problems of poverty, cultural and political change.
- First colonization and then globalization have transformed developing countries in a few generations.
- Women’s roles in society directly affect how HIV is transmitted.
- Failure to take cultural differences into account may compromise Western aid efforts.