MTN-009:

Why It's Important to Understand ARV Resistance in Our Communities

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MTN-009: Prevalence of HIV-1 Drug Resistance within a Female Screening Population for HIV Prevention Trials

A woman comes to the clinic interested in HIV prevention.

She wants to be a part of VOICE...

...but she is already infected with HIV.

How long ago did she get infected?

What stage of infection is she in?

Has she had risk behaviors or exposures to antiretroviral drugs?

Does she have detectable drug resistance?

Does she have low frequency drug resistance?

Why is it important to know?

Resistance and HIV Prevention

- Resistance to current ARVs used for treatment could decrease effectiveness of products used for prevention

- MTN-009 will help understand current status of resistance in population of potential users of ARV-based prevention products

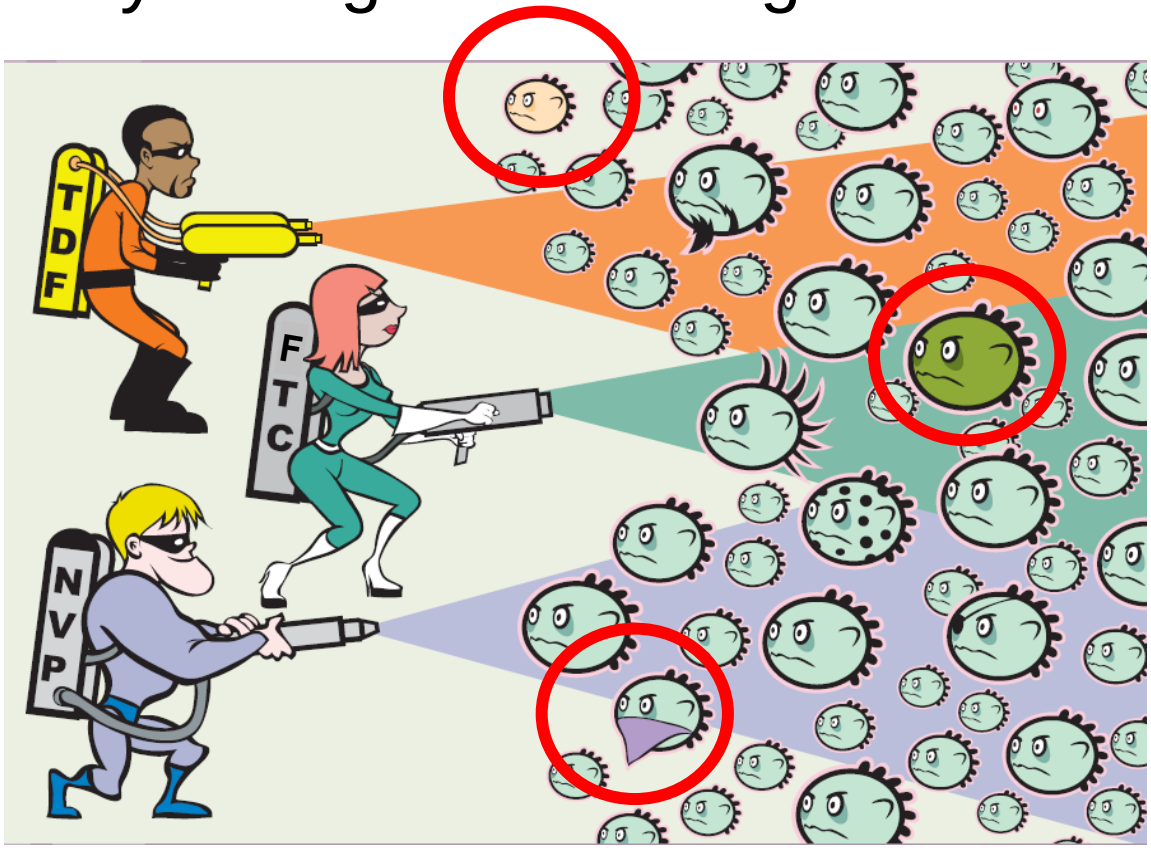
Widespread drug resistance can have a significant public health impact

Outline

- Drug resistance in HIV-positive, treatment-naïve women
- Current drug resistance surveillance efforts in Sub-Saharan Africa
- Contribution of MTN-009

What is HIV drug resistance?

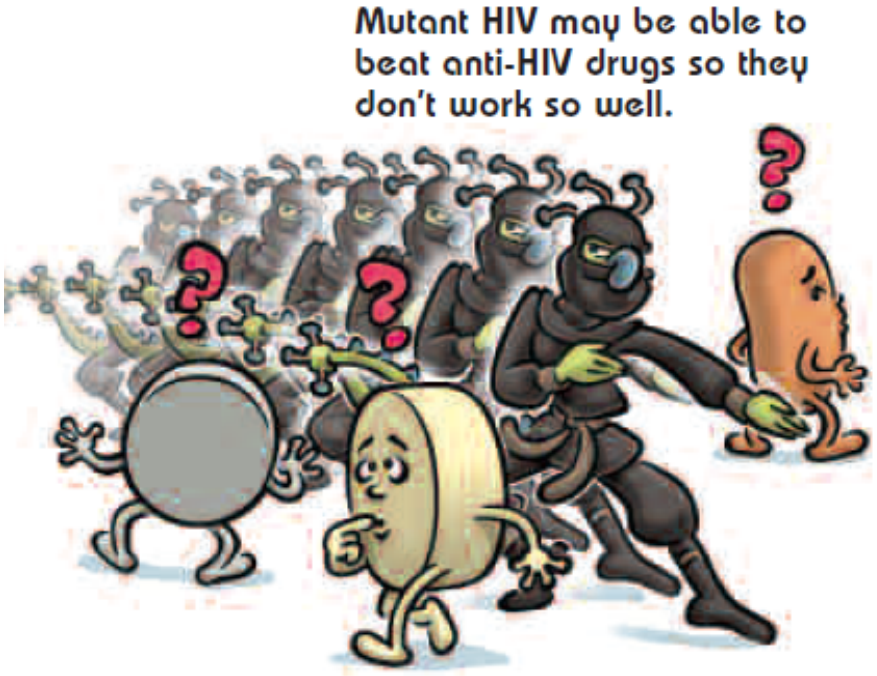
- Loss of effectiveness of one or more ARV
- Caused by changes in HIV's genetic material.



www.thebody.com

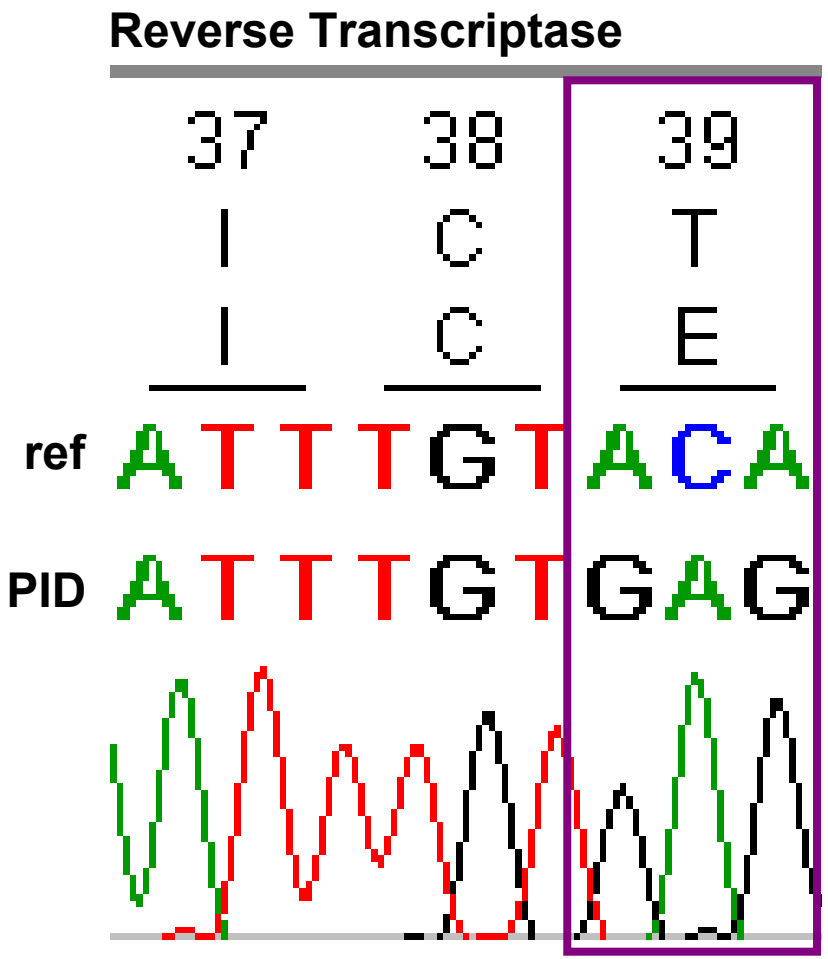
How would a woman who has never taken ART get drug resistance?

- Polymorphisms
- Selection
- Transmission



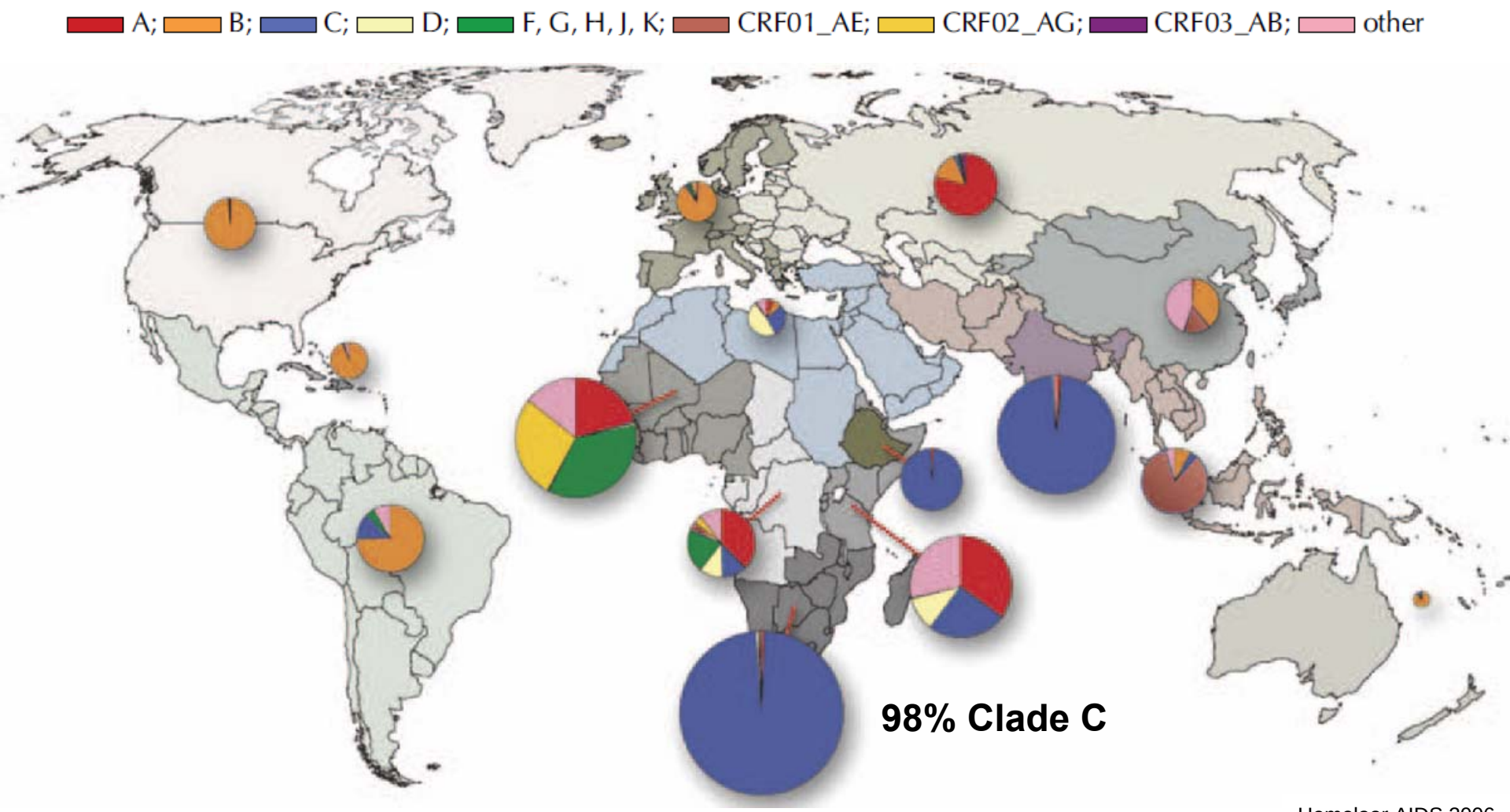
Polymorphisms

- Naturally occurring differences in HIV-1 genome compared to a “reference” sequence (e.g. subtype B HXB2)
- Impact of polymorphism may be
  - Nothing
  - May cause resistance (uncommon)
  - Could facilitate selection of resistance



e.g. T39E

Subtype Distribution



Hemelaar AIDS 2006

Impact of Subtype C polymorphisms on Resistance

- K65R selected more rapidly in Sub C (Coutsinos JV 2009, Doualla-Bell AAC 2006)
- Increased replication capacity of some TAMS in Sub C vs B (Armstrong JV 2009)
- I36 in protease confers higher rates of PI treatment failure (Lisovsky AAC 2010)
- Different susceptibility to integrase inhibitors, entry inhibitors (Bar-Magen AIDS 2010, Gonzales AIDS Res Hum Retroviruses 2010)

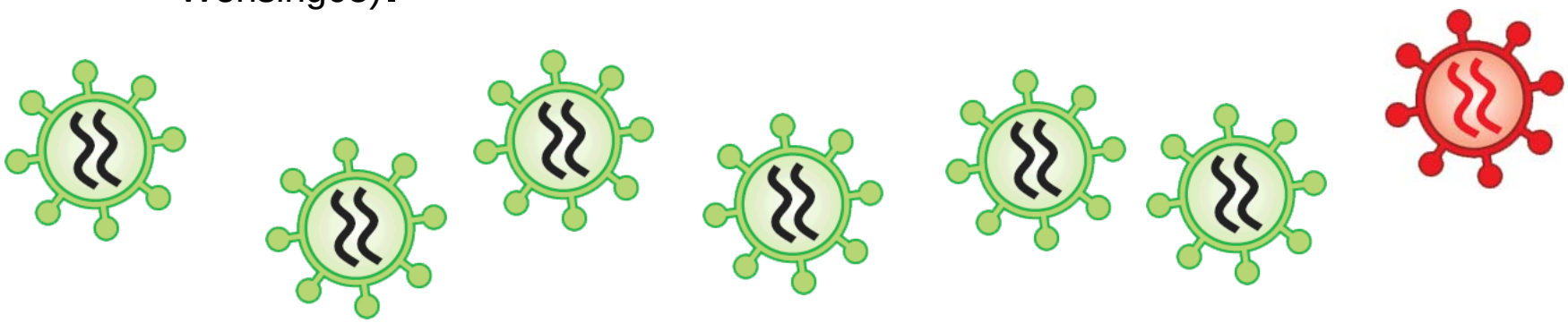
Resistance from ART

- Selection = individuals who are using ARVs may develop drug resistance if ARVs do not completely stop HIV replication

  - Drug/product sharing
  - ART fails to protect against infection
  - ART fails to decrease viral load
  - PMTCT – unknown status

Transmitted Resistance

- Transmission = an individual becomes infected by someone who has drug resistant virus
  - Where ART is widely used, between 5 and 20% of new HIV infections include virus that have drug resistant mutations (Grant02; Little02; Wensing05).



WHO Threshold Survey

- Most drug resistance data from Africa is from WHO resistance threshold survey
- Classifies country as <5%, 5-15%, or >15% based on 47 specimens from people recently diagnosed with HIV
- <5% does not mean absence of resistance
  - e.g. 4.2% of drug naïve pregnant women in South Africa had evidence of resistance (Pillay Antivir Ther 2008)

PASER

- **P**harm**A**ccess African **S**tudies to **E**valuate **R**esistance
- Monitoring acquired and transmitted resistance in sub-Saharan Africa:
  - Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe
- Preliminary results from chronically infected population:
  - 98% subtype C
  - **13/242 samples (5.4%)** from people who were ARV-naïve demonstrated HIV drug resistance mutations

SATuRN

- **S**outhern **A**frican **T**reatment and **R**esistance Network and the Stanford HIV Drug Resistance Database
- Mirror of the Stanford Resistance Database – bioafrica.net
- A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance
- Compiles/analyzes data

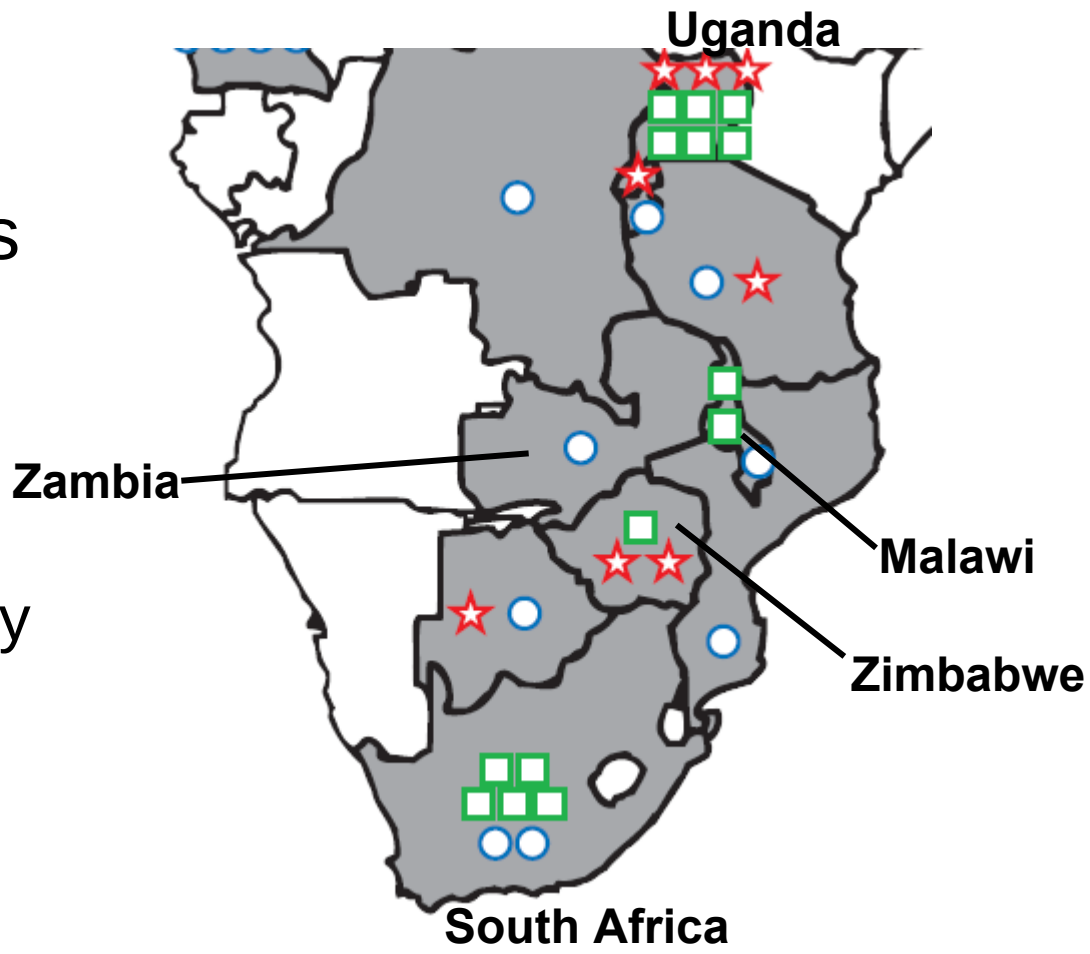
Resistance Surveillance

Country	WHO (Year)	Other (Year of Study)
South Africa	<5% (2004)	4.2% (2004) (Pillay)
Malawi	<5% (2005)	-
Uganda	<5% (2006)	5.8% (2009) (Rakai)
Zambia	<5% (2008)	5.7% (2010) (PASER)
Zimbabwe	<5% (2008)	-
Meta-analyses (Africa overall)	-	5.5% (2003) (WATCH) 5.6%* (2008) (PASER)

*0-5.6% NNRTI; 0-3.7% NRTI

Limitations

- Limited data and number of studies
- Small sample sizes (n = 20-128)
- Substantial differences in
  - Assay methodology
  - Time period
  - Population studied



PASER 2008

Unanswered Questions

- What is the risk of transmitted drug resistance to women who use TFV or Truvada for prevention?
- Do threshold surveys underestimate the level of transmitted resistance by not accounting for low frequency variants?

MTN-009 Study Purpose

- To determine prevalence of drug resistance in population of women interested in VOICE **who test HIV positive prior to screening**

- First study to evaluate resistance data in context of:
  - **Infection status:** viral load/CD4 T cell counts
  - **Risk assessment:** ACASI questionnaire
  - **Timing of infection:** recent vs chronic

MTN
microbicide trials network

Why evaluate infection status?

- Who is coming to the clinic for HIV prevention products?
- What stage of infection is she in?
  - CD4 T cell counts
  - Viral Load
  - Fast track for treatment?

Why Test for Recent HIV Infection?

- Those infected recently are more infectious
  - Generally have high viral loads
  - Could have transmitted drug resistance
  - Could transmit drug resistance to others
- Do those with recent HIV infection have greater prevalence of drug resistance?
  - Mutations could fade over time if untreated

Why Behavioral Questionnaire?

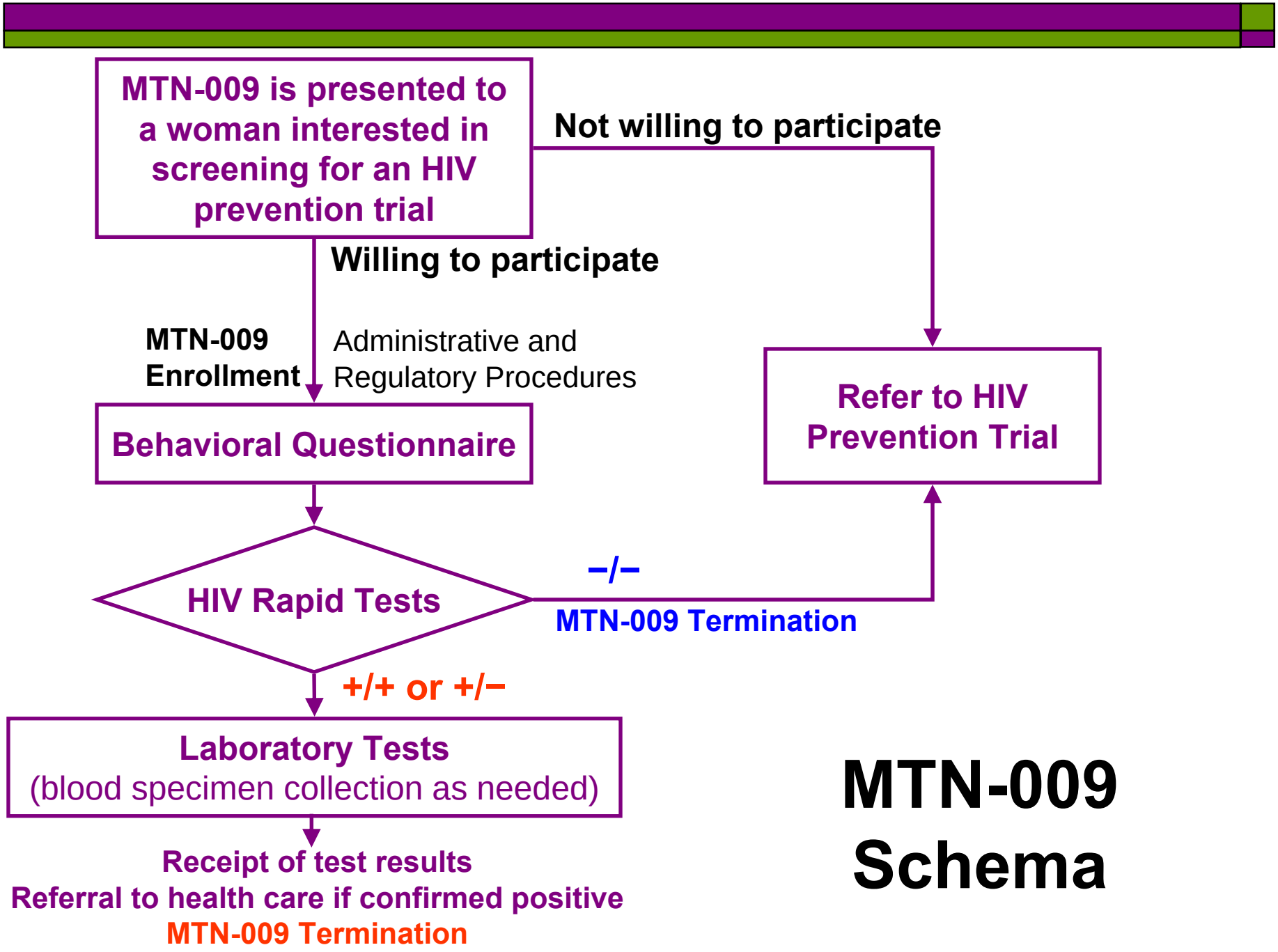
- Short ACASI questionnaire
- Who is coming to the clinic for screening?
  - Perceived risk of HIV infection
  - Ever tested for HIV infection
  - Sexual risk behaviors of self/partner
  - Drug use/ARV exposures
  - Interest in trial participation
- Better characterize HIV infection/HIV resistance in both positive/negative participants

MTN-009 Study Summary

Title	Prevalence of HIV-1 Drug Resistance within a Female Screening Population for HIV Prevention Trials
Sample Size	Approx 1000 (350 evaluable positive)
Population	Women presenting for screening for HIV prevention trials
Sites	South African MRC HIV CTU Durban (7)
Design	Cross-Sectional
Duration	Approx 1-3 study visits/participant Projected 2 yr of accrual

Study Hypothesis

- The prevalence of HIV drug resistance in the population of women identified as HIV-positive during screening procedures for HIV prevention trials will be low and underestimated by standard genotyping methods.



MTN-009 Schema

Current Status of MTN-009 (4Oct10)

Site	Screened/ Enrolled*	HIV Infected	% Infected
Botha's Hill	28	10	36%
Chatsworth	29	11	38%
Isipingo	4	2	50%
Overport	40	20	50%
Tongaat	21	8	38%
Umkomaas	10	1	10%
Verulam	10	2	20%
TOTAL	**142**	**54**	**38% (avg)****

*To date, no participant has refused enrollment

**Estimate was 35% (350 positive/1000 participants)

What will MTN-009 add?

- Focus on women who present for screening in microbicide trials
  - Provide baseline information for analysis of data from MTN prevention trials and for our study population
  - Allow better targeting and implementation of a microbicide should a parent trial identify one as successful

What will MTN-009 add?

- Better characterizes resistance
  - Provide data about behavior and personal assessment of HIV infection risk
  - Estimate how recently infection occurred
  - Determine degree of immunodeficiency (viral load, CD4 T cell counts)
  - Detect low-frequency mutants (<20%) missed by standard genotype

Acknowledgements

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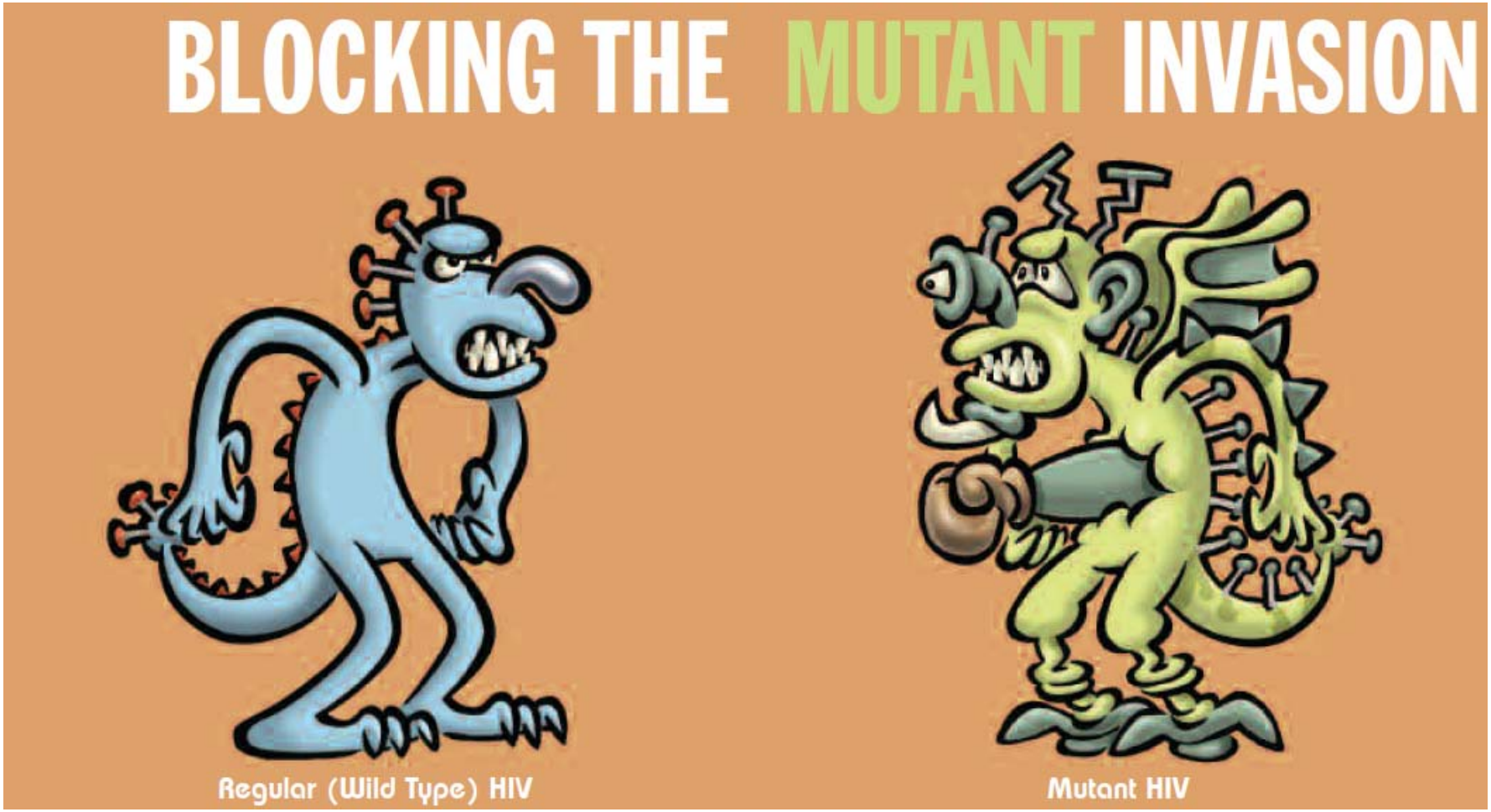
Thank You!


BLOCKING THE MUTANT INVASION
Regular (Wild Type) HIV
Mutant HIV