HIV in young women in KwaZulu-Natal: Imperative for their Inclusion in HIV Biomedical research studies

Presented by: **Ayesha BM Kharsany**

HIV in young women in KwaZulu-Natal: Imperative for their Inclusion in HIV Biomedical research studies

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Overview of Presentation

- **Research priorities, studies and Rationale**

- **Surveillance**

- **Phylogenetic studies**

- **HIV Transmission Networks**

- **Genital Inflammation**

- **Vaginal flora**

- **Conclusions**

CAPRISA Research Priorities

To undertake *globally relevant & locally responsive* research that contributes to understanding HIV pathogenesis, prevention & epidemiology as well as TB-HIV treatment

Understand the epidemiology of HIV in young women

HIV in South Africa
Disproportionate burden of HIV in young women

Southern & eastern Africa have 70% of the world's HIV burden

HIV in 15–24 year men and women (2008–2011)

Young women have up to 8 times more HIV than men
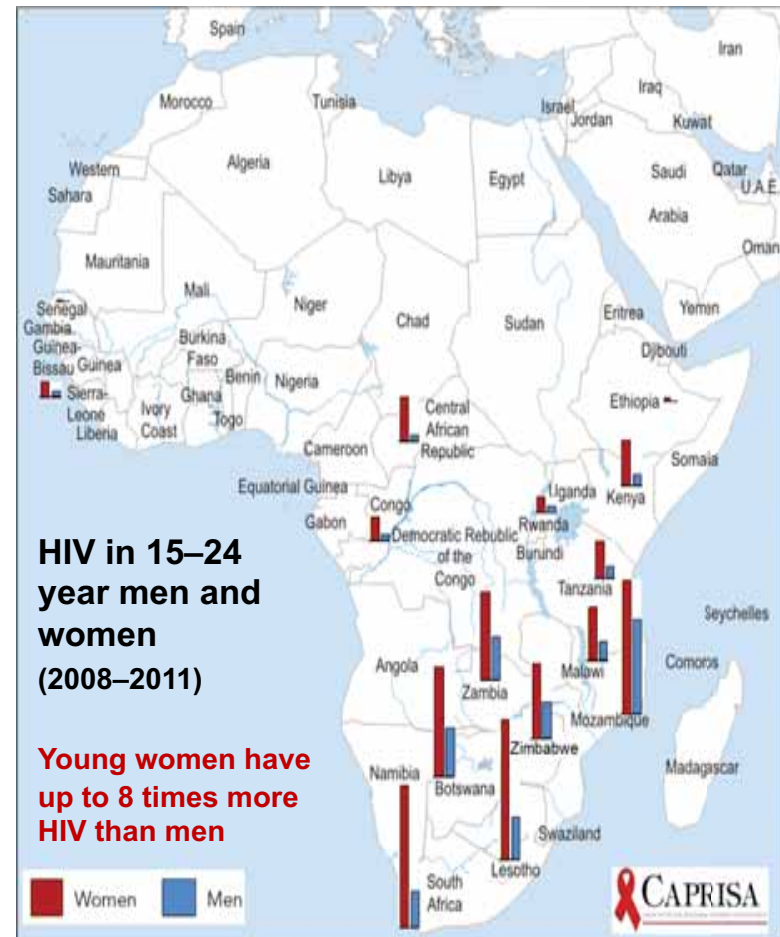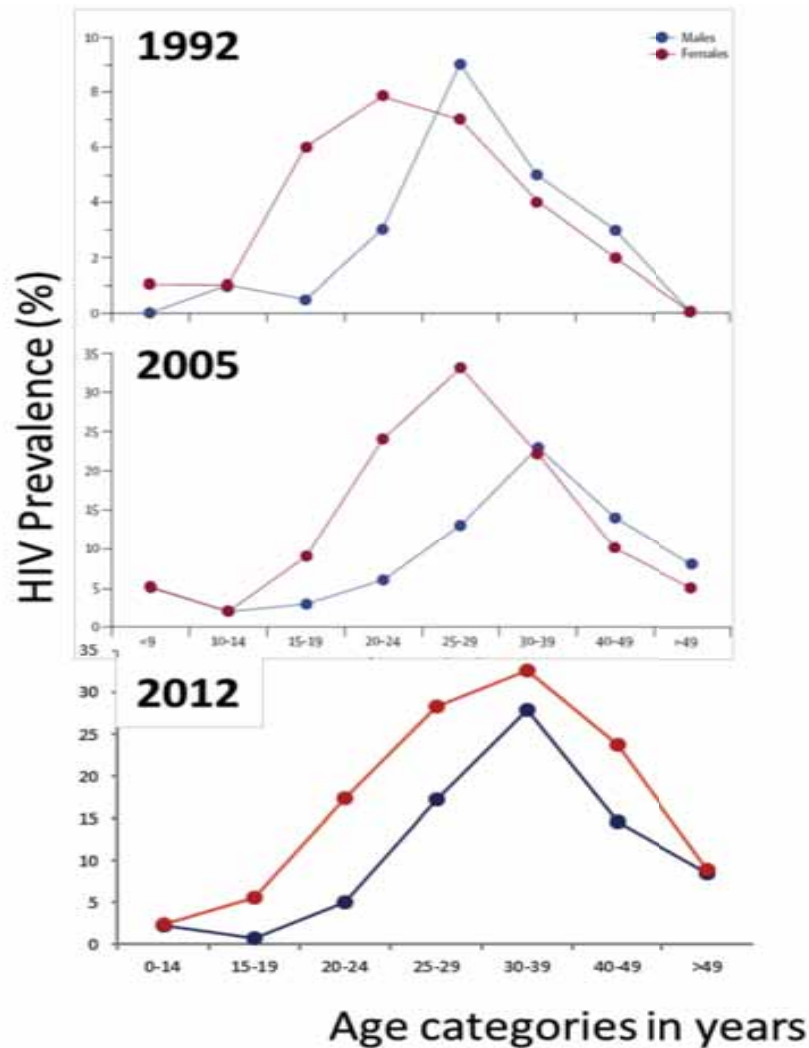
Trends in HIV in pregnant women in rural KZN 2001-2013

Age Group (Yrs)	HIV Prevalence (n=4818)
≤16	11.5%
17-18	21.3%
19-20	30.4%
21-22	39.4%
23-24	49.5%
>25	51.9%

Age group (Yrs)	HIV Prevalence %		
	Pre-ART 2001-2003	Early ART 2004-2008	Current ART 2009-2013
<20	22.5	20.7	17.2
20-24	45.5	44.2	37.9
25-29	47.9	58.8	57.6
30-34	26.7	55.5	59.9
≥35	27.4	30.8	53.4
Total	35.3	39.0	39.3

Key findings

- **Pregnant women <20 years old**

  >30%

- **HIV prevalence consistently high**

  30% and 40%

  by age 24; 1 in 2 HIV positive

- **HIV prevalence in the <20 year age group** >20%

- **Increase in partner's age**
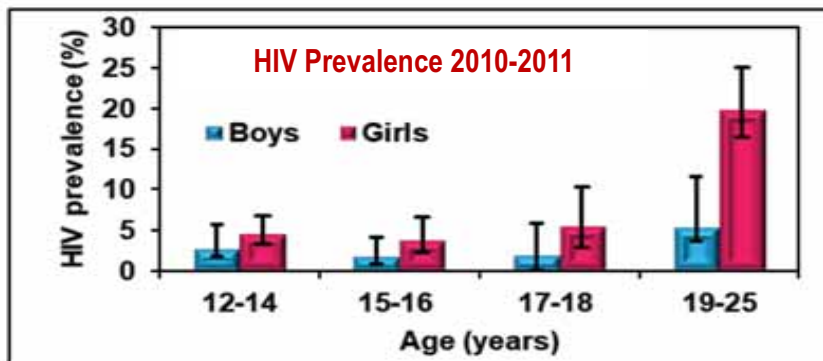 Increase in HIV prevalence in young women

- **HIV incidence**

  11.2%

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Trends in HIV in high school students in rural KZN

Age Group (Yrs)	HIV Prevalence 2010 (% 95% CI)	
	Boys (n=1262)	Girls (n=1423)
≤15	**1.0** (0.0 - 2.2)	**2.6** (1.2 - 4.0)
16-17	**1.1** (0.2 - 2.0)	**6.1** (2.6 - 9.6)
18-19	**1.5** (0 - 3.7)	**13.6** (9.0 - 18.1)
≥20	**1.8** (0 - 3.9)	**24.7** (6.3 - 43.1)
Overall	**1.4** (0.9 - 1.9)	**6.4** (4.6 - 8.3)

Source: Abdool Karim Q, et al. Sexually Transmitted Infections 2014, 90:620-626.

*Source: Kharsany AB et al BMC Public Health 2012,**12**:231*
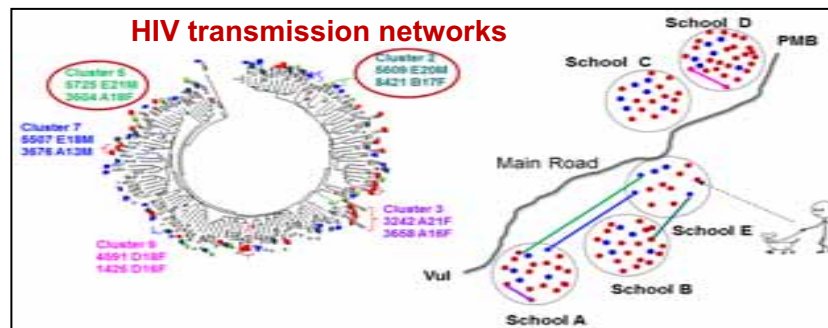
Source: Kharsany AB. et al AIDS Research and Human Retroviruses 2014,30:956-965

Key findings

- Learners were sexually active

  1 in 4

- HIV prevalence

  High across all ages

  Higher in girls vs boys

- Girls with older sex partners

  3 to 4 times more likely to be HIV +

- Clues on HIV transmission

  Limited in and across schools

- Possible introductions

  Community

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# Challenges to understanding HIV acquisition in adolescent girls and young women

- **Biological and structural factors**

- **Risk behaviors of young women**
    - **Low sexual frequency but high risk sex**
    - **Few have multiple concurrent partners**
    - **Why?**

- **Age-disparate relationships as a key contributor to HIV acquisition**

    - **Evidence**

        - Consistent in CAPRISA studies

        - Conflicting with literature

            - Bias with study design

            - Analysis bias

            - Reliability of self reported data

            - Definitions

Young women at high HIV risk
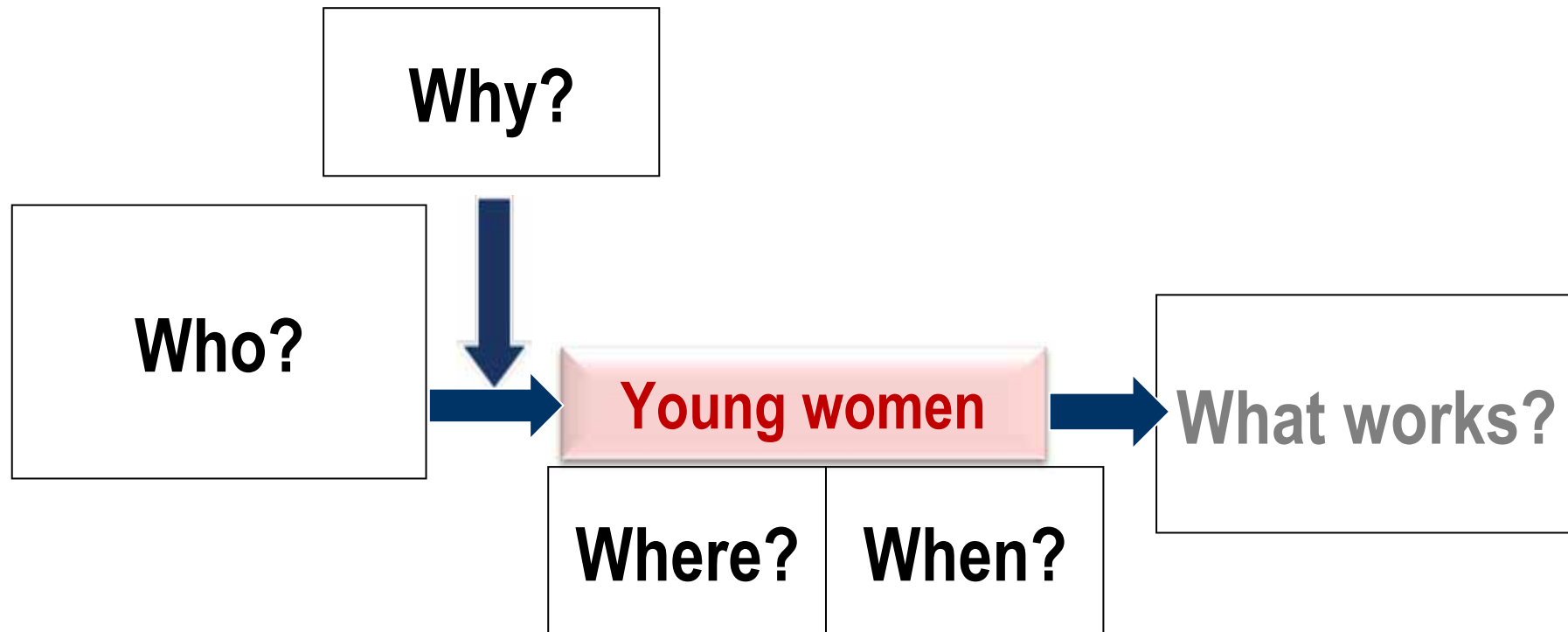
Community Based Surveillance

HIPSS
HIV Incidence Provincial
Surveillance System Project

Study site
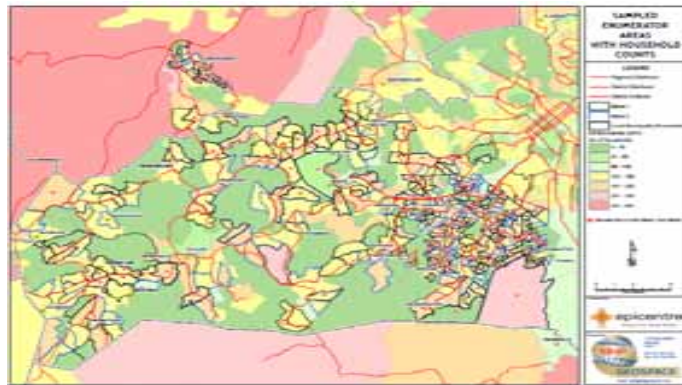
- **Purpose:** Evaluate population impact of programmatic scale-up of combination prevention efforts in a "real world", non-trial setting in rural KZN

- **Study objectives:** Measure HIV prevalence and incidence in relation to ART and plasma viral load

- **Study Location:** 2 Sub-districts of uMgungundlovu district, KZN, SA
  - Population of ~370 000
  - Males   ~176 418 / Females ~191 515
  - High levels Poverty / Unemployment
  - Highest HIV burden district in SA
  - (SA DOH_ANC prevalence-40.7% in 2012)

Source: Kharsany AB et al. BMC Public Health 2015,15:1149.

School Based Surveillance

CANS Adolescent Network studies
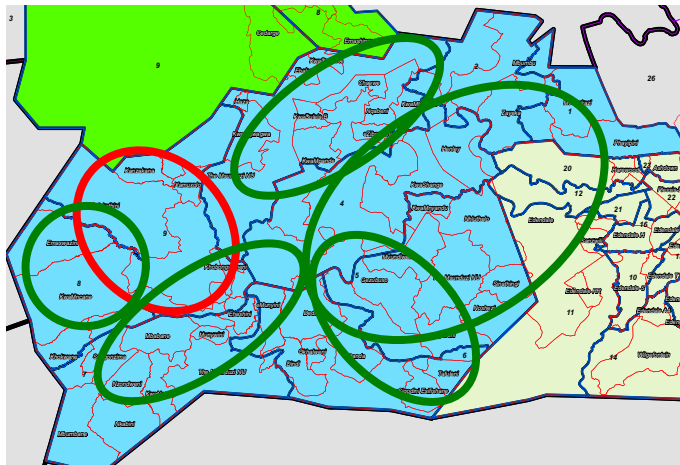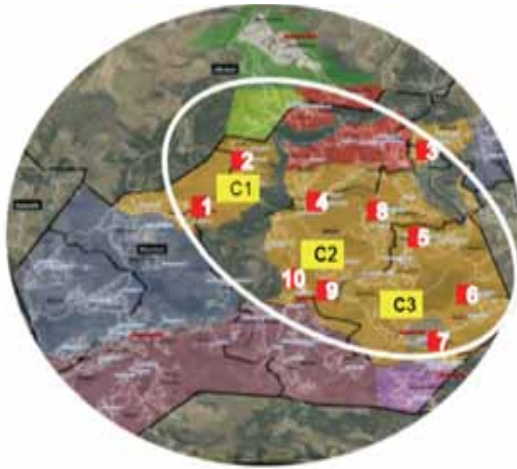
- **Purpose:** To understand the HIV transmission dynamics and sexual networks that adolescent may belong to, potentially increasing their risk for HIV infection.

- **Study objectives:** To identify HIV transmission linkages that contribute to the source of infection in adolescent girls in rural KZN

- **Study Sites :** Specified geographical location to maximise density and coverage
  - All high schools n=+/-8000
  - Facilities – out of school pregnant girls n=+/-1000
  - Out of school high risk adolescent boys (RDS) n=+/- 1000.

Source: Kharsany et al :Identifying sources of HIV infection in adolescent girls in rural South Africa National Institutes of Health,RO1, R01HD083343 (Multi-PI: Kharsany and Kohler).
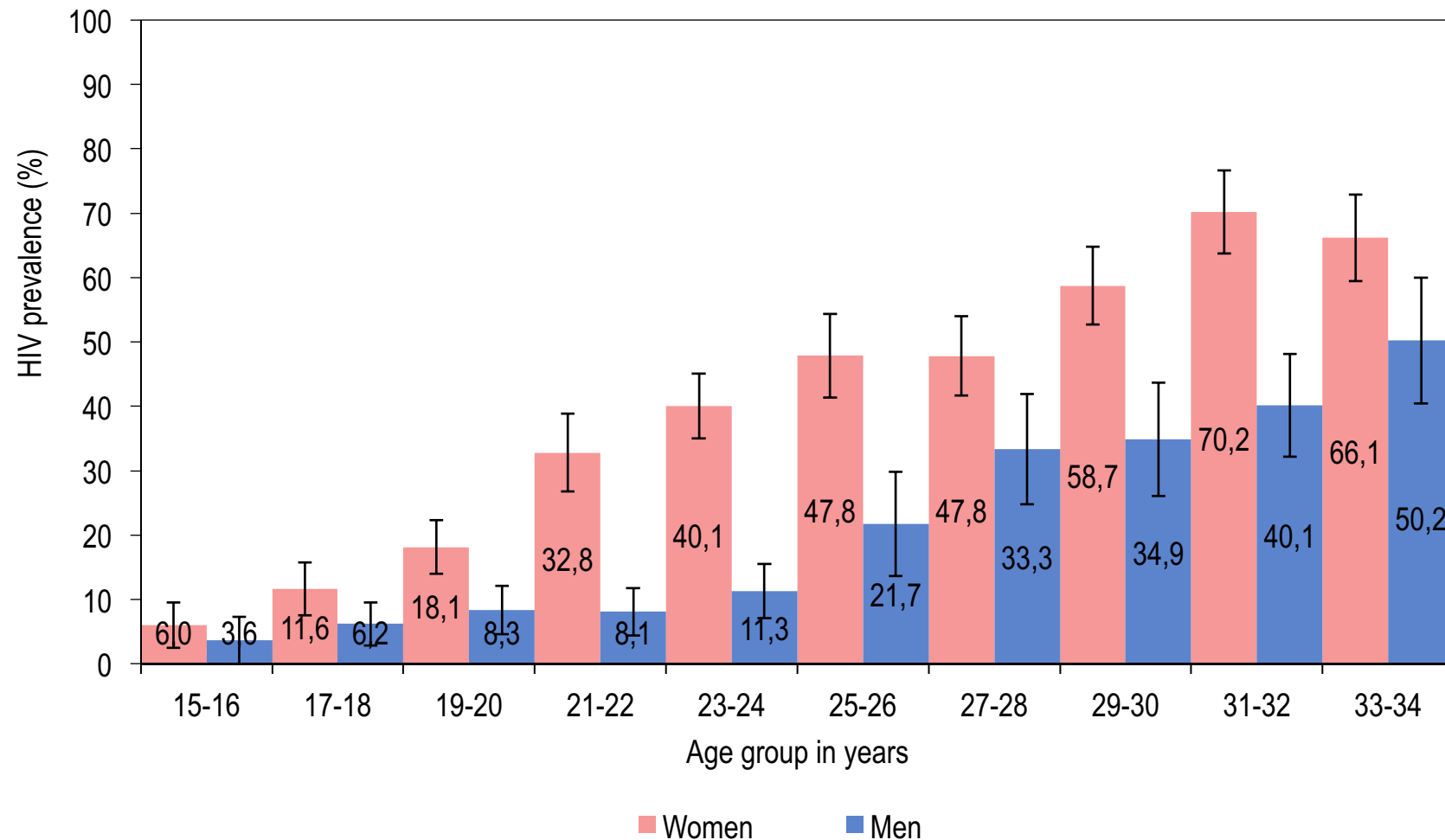
Community-wide phylogenetic study

- **Cross-sectional multi-stage random sampling**

- **Duration: 2014 - 2016**

- **86% consent rate**

- **People tested for HIV: 9 812**

- **HIV positive: 36.3%** (CI: 35-38) (n=3,969)

- **Knew HIV+ status: 59.8%** (n=2,337)

- **On ARVs: 42.3%** (n= 1,590)

- **Viral load >1000: 47.1%** (n= 1,847)

HIV sero-prevalence by age and gender in a rural and peri-urban community in KZN, South Africa, 2014-2015
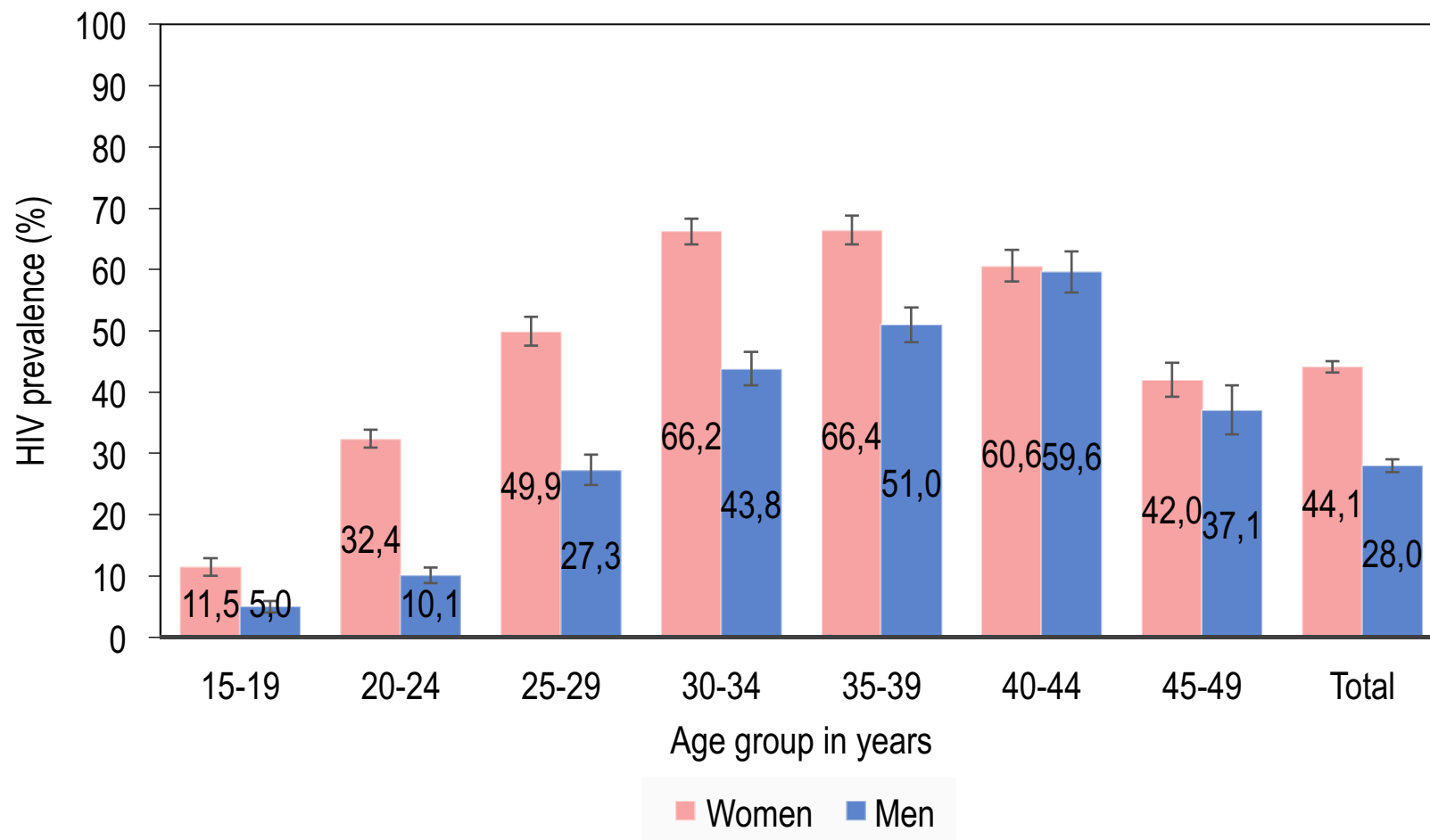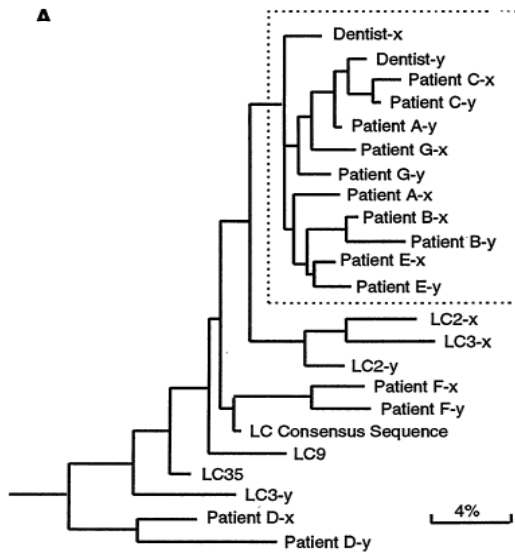
HIV sero-prevalence in young men and women in a rural and peri-urban community in KZN, South Africa, 2014-2015

Phylogenetic analyses to assess HIV genetic diversity for identifying linked viruses

A

Dentist-x
Dentist-y
Patient C-x
Patient C-y
Patient A-y
Patient G-x
Patient G-y
Patient A-x
Patient B-x
Patient B-y
Patient E-x
Patient E-y
LC2-x
LC3-x
LC2-y
Patient F-x
Patient F-y
LC Consensus Sequence
LC9
LC35
LC3-y
Patient D-x
Patient D-y

4%

Individual linkage analysis

Transmission linkages in 5 patients who became infected with HIIV while receiving care from a dentist with AIDS

Source: Ou CY et al : Science 1992, 256:1165-1171.

C151
C115
C116
C99-K103N
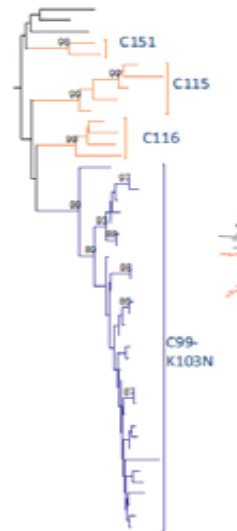
MSM epidemic in Montreal

Unique transmission clusters three small clusters and one large cluster with K103N resistance mutation

Source: Brenner B et al AIDS. 2013;27(7): 1045-57.

C

Color key for geo-regions
R1   R7
R2   R8
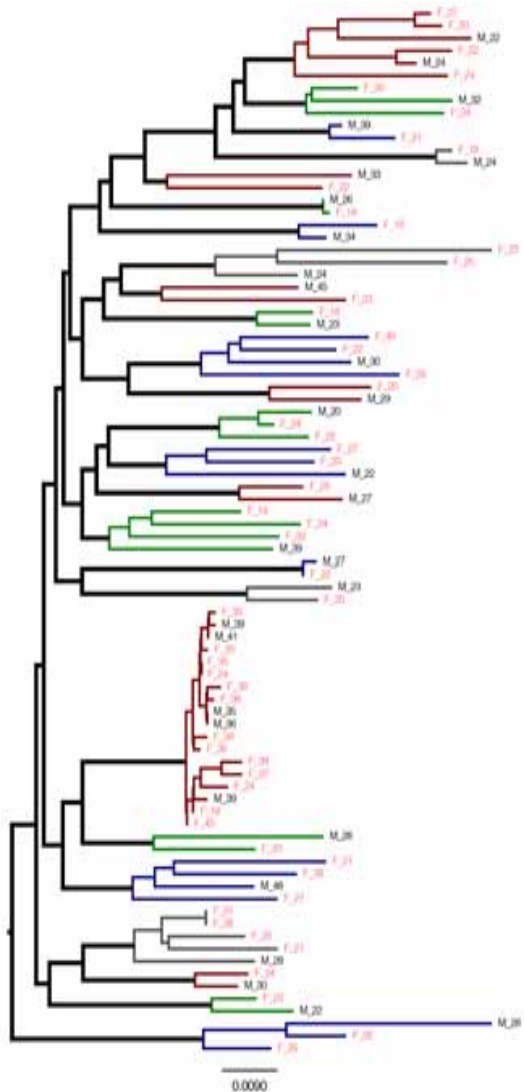R3   R9
R4   R10
R5   R11
R6

0.02
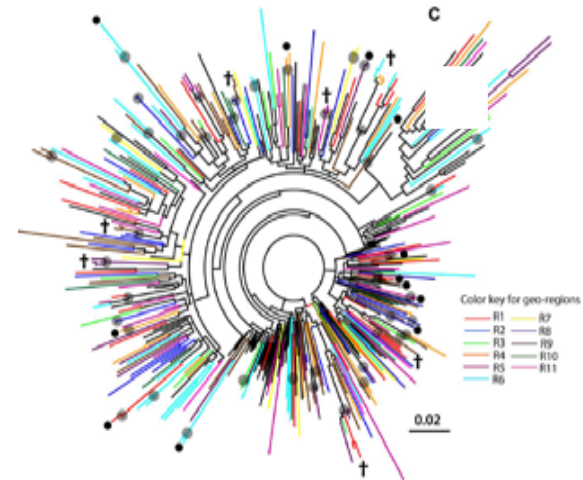
Rakai, Uganda

Significant viral introductions
39% within households
40% from extra household contacts / outside communities.
Localised key population drive the epidemic

*Source: Grabowski MK, et al. PLoS Med. 2014;11(3):e1001610.*

Phylogenetics to map HIV transmission

- **1,589 of 1847 viruses sequenced**

- **_pol_ region**

- **Maximum likelihood tree
  Branch support > 90%
  Genetic diversity < 4,5%**

- **Phylogenetic linkage = probable recent transmission as those with more established infection were on ART**

- **202 phylogenetically linked clusters of 469 sequences**
  - 168 with 2 individuals
  - 22 with 3 individuals
  - 8 with 4 individuals
  - 1 with 5 individuals
  - 2 with 6 individuals
  - 1 with 18 individuals

Phylogenetic analysis: cluster linkages

90 clusters (Male-Female linkages) –123 females linked to **103** males (188 possible pairings)
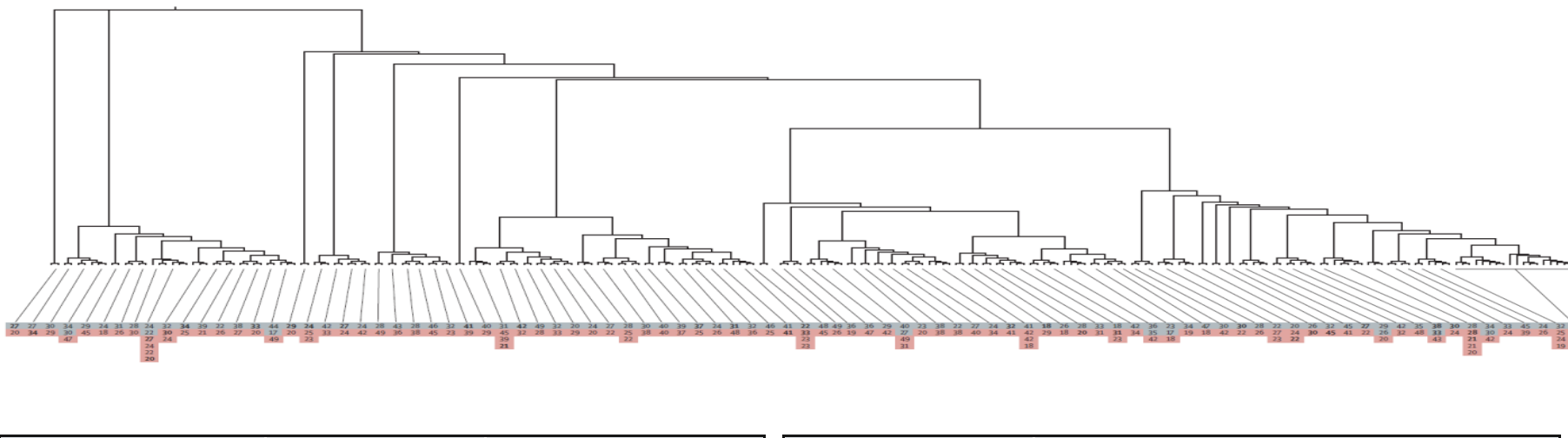
	Women	Men
Median VL	16,629c/ml	31,000 c/ml
on ARVs	4.1%	4.9%
Known HIV+	38.9%	26.2%

Women age group	Age difference with male partners	
16-20	11.5 yrs	**< 25: 8.7 yrs**
21-25	7.0 yrs	
26-30	1.5 yrs	
31-35	1.7 yrs	**≥ 25: 1.1 yrs**
36-40	0.7 yrs	

Phylogenetic pairing and HIV-1 prevalence

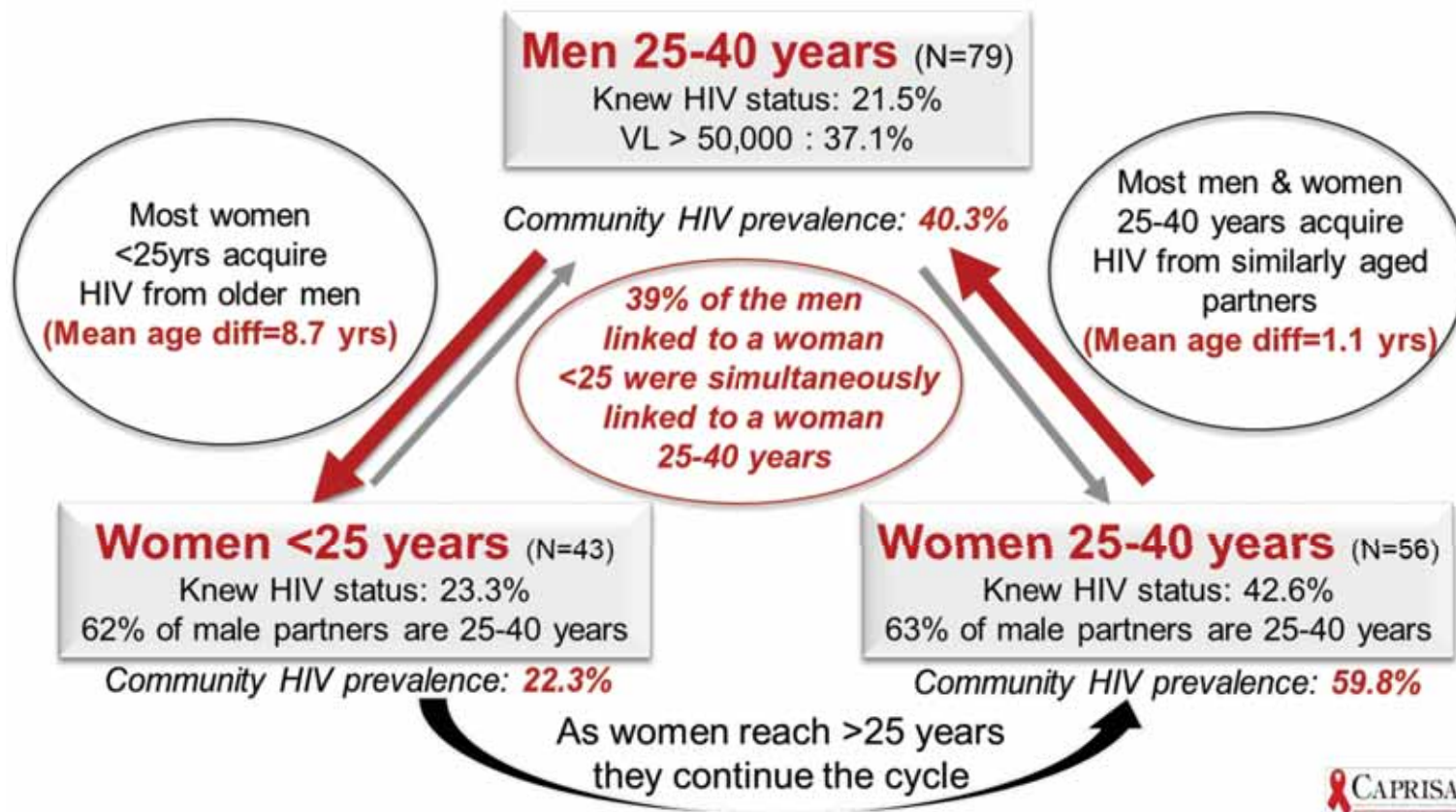| Females Community HIV prevalence	Males Community HIV prevalence			Total
	<25yrs (7.6%)	25-40yrs (40.3%)	40-49yrs (47.2%)	
<25 yrs (22.3%)	18	**37**	5	60
25-40 yrs (59.8%)	13	**58**	21	92
40-49 yrs (50.1%)	2	24	10	36
Total	33	**119**	36	188

- Pairing across all age groups, but the highest linkage is of men 25-40 (group that has the highest prevalence of viraemia including PVL >50 000 c/ml

- HIV-1 transmission occurs from high-prevalence to low prevalence, unless there are super-spreaders

Why: HIV transmission networks in rural South Africa
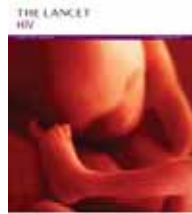
Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study

Tulio de Oliveira*, Ayesha B M Kharsany*, Tiago Gräf, Cherie Cawood, David Khanyile, Anneke Grobler, Adrian Puren, Savathree Madurai, Cheryl Baxter, Quarraisha Abdool Karim, Salim S Abdool Karim
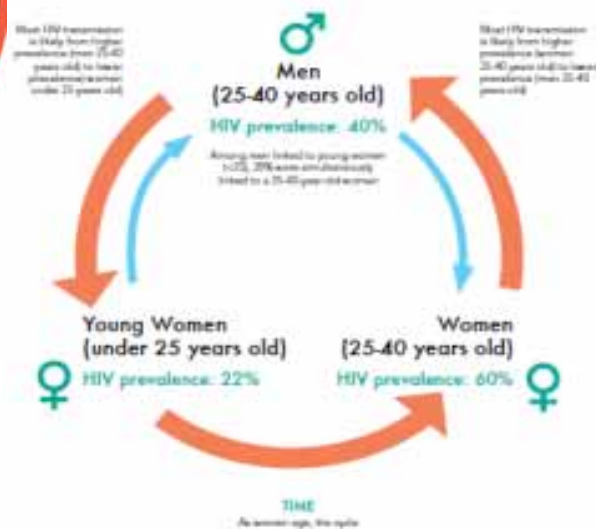
Men 25-40 years (N=79)
Knew HIV status: 21.5%
VL > 50,000 : 37.1%

Community HIV prevalence: 40.3%

Most women <25yrs acquire HIV from older men (Mean age diff=8.7 yrs)

39% of the men linked to a woman <25 were simultaneously linked to a woman 25-40 years

Most men & women 25-40 years acquire HIV from similarly aged partners (Mean age diff=1.1 yrs)

Women <25 years (N=43)
Knew HIV status: 23.3%
62% of male partners are 25-40 years
Community HIV prevalence: 22.3%

Women 25-40 years (N=56)
Knew HIV status: 42.6%
63% of male partners are 25-40 years
Community HIV prevalence: 59.8%

As women reach >25 years they continue the cycle

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UNAIDS AIDS Update 2016
Get on the Fast- Track
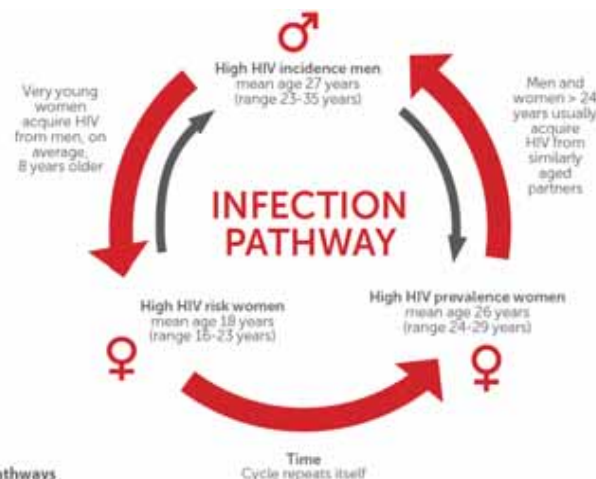**T**he Life –cycle approach to HIV

LET OUR ACTIONS COUNT
SOUTH AFRICA'S NATIONAL STRATEGIC PLAN ON HIV, TB and STIs 2017-2022

Goal 1: Accelerate prevention in order to reduce new HIV and TB infections and new STIs.

– Breaking the cycle of transmission

The NSP sets out intensified prevention programmes that combine biomedical prevention methods, such as medical male circumcision (MMC) and the preventive use of antiretroviral drugs (ARVs) and TB medication, with communication designed to educate and encourage safer sexual behaviour in the case of HIV and STIs, and environmental interventions to control TB infection.

Men (25-40 years old) HIV prevalence: 40%

Young Women (under 25 years old) HIV prevalence: 22%

Women (25-40 years old) HIV prevalence: 60%

TIME

INFECTION PATHWAY

High HIV incidence men mean age 27 years (range 23-35 years)

Very young women acquire HIV from men, on average, 8 years older

Men and women > 24 years usually acquire HIV from similarly aged partners

High HIV risk women mean age 18 years (range 16-23 years)

High HIV prevalence women mean age 26 years (range 24-29 years)
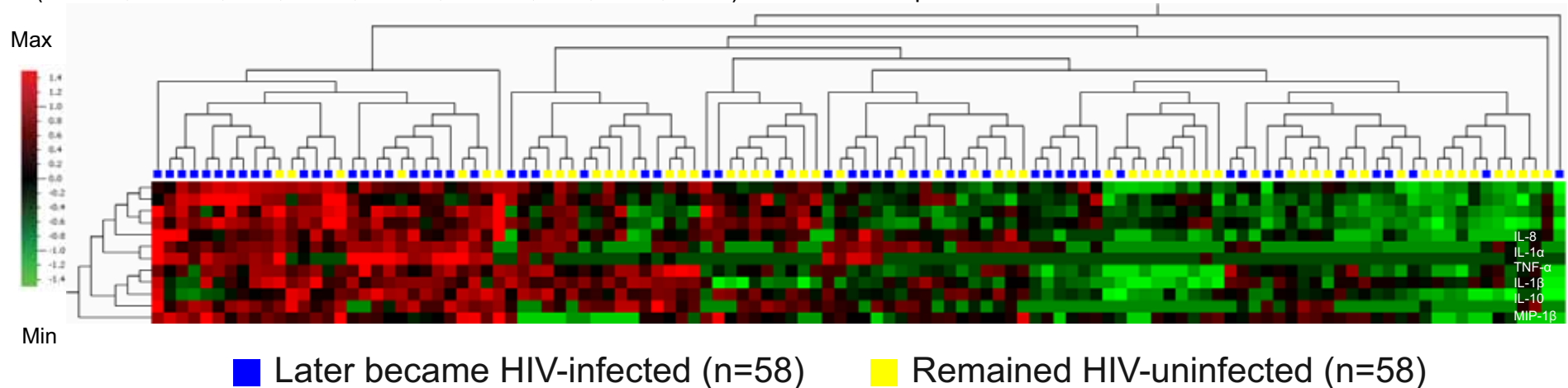
Transmission pathways

Time Cycle repeats itself

Important public health benefit

Why: Vaginal Microbiome : genital inflammation

Cytokine and chemokine responses

(MIP-1a, MIP-1b, IL-8, IP-10, TNF-a, MCP-1, IL-6, IL-1a, IL-1b) above the 75th percentile

Later became HIV-infected (n=58)   Remained HIV-uninfected (n=58)

Women who later became HIV-infected had pre-infection genital inflammation – what is the cause?

Only **20%** of HIV infections could be attributed to an STI
T. vaginalis was the most strongly predictive of genital inflammation

Source: Masson L, Passmore ɑ ee aM↓ Nh Infece Dis 2015,61:2u0c2u M

Association between genital inflammation and HIV acquisition

	HIV+	HIV-	Total
Genital inflammation present*	**19**	**6**	25
Genital inflammation absent	**39**	**52**	91
Total	58	58	116

Odds Ratio 3.2 (95% CI: 1·3 – 7.9), p-value 0.014

*Women with 5 or more **pro-inflammatory cytokines or chemokines** (MIP-1a, MIP-1b, IL-8, IP-10, TNF-a, MCP-1, IL-6, IL-1a, IL-1b) above the 75th percentile

Significant after adjusting for age, urban/rural, condom use, hormonal contraceptives, number of sex acts, number of returned used applicators, HSV-2 status

Vaginal Microbiome
16s DNA sequencing of genital swab samples
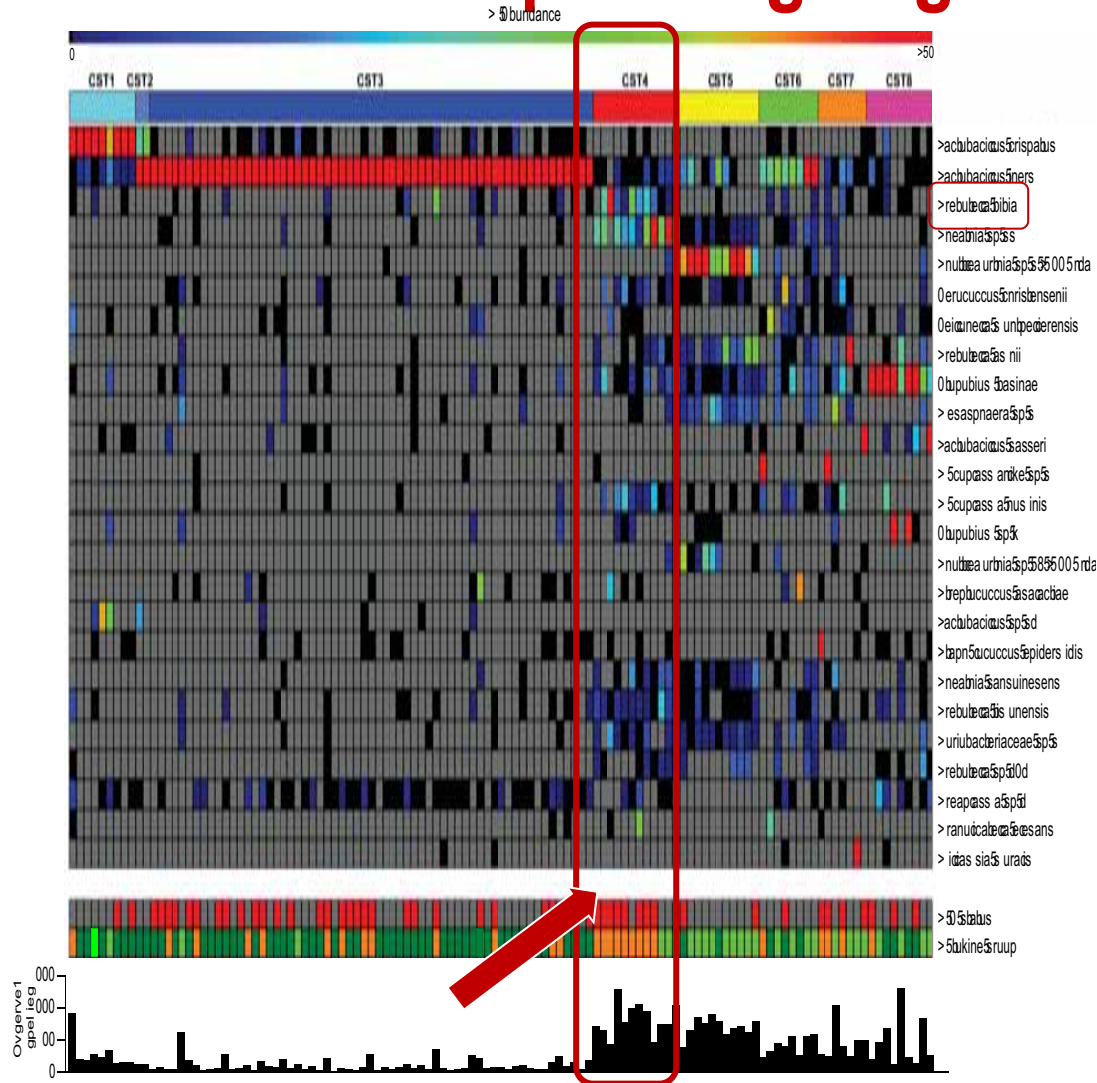
Over 3 million sequences

1368 species identified

- Predominance of Cluster Community State Type (CST) 4 related organisms

- *Prevotella bivia*

- Linked with
  - genital inflammation
  - HIV acquisition

Prevotella bivia is strongly associated with genital inflammation and HIV acquisition

	P. bivia+ OR*	P value
GI	19.2 (95% CI: 4.0-92.4)	p<0.001
HIV+	12.7 (95% CI: 2.1-77.8)	p=0.006

adjusted odds ratio

22 women were HIV positive & had inflammation – 9/22 (41%) had *P. bivia*

Women with *P. bivia* were **19 times** more likely to have genital inflammation and **13 times** more likely to acquire HIV

Proteomics: Identification of Vaginal microbial groups
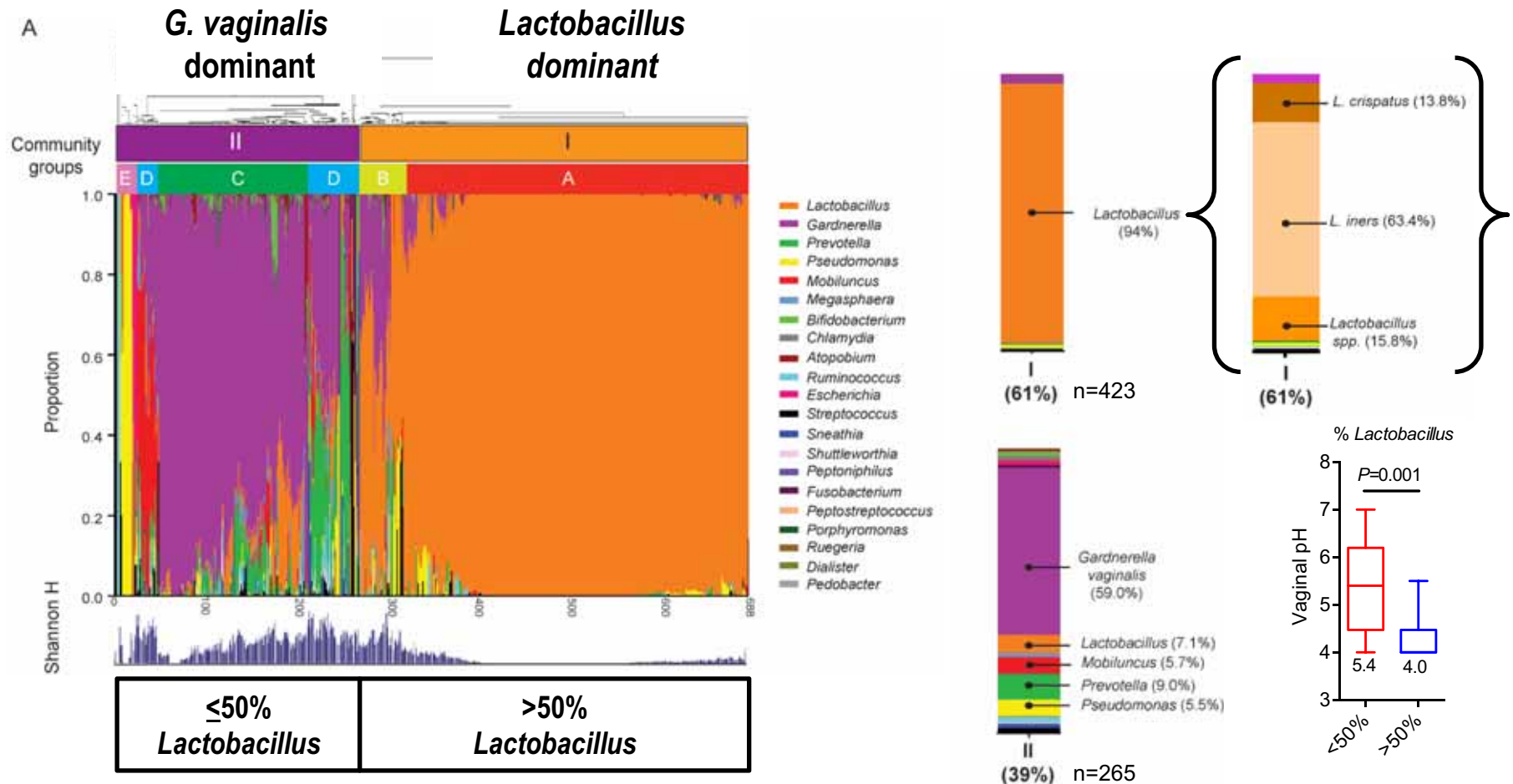
Effectiveness of Tenofovir gel against HIV amongst women with Lactobacillus dominance
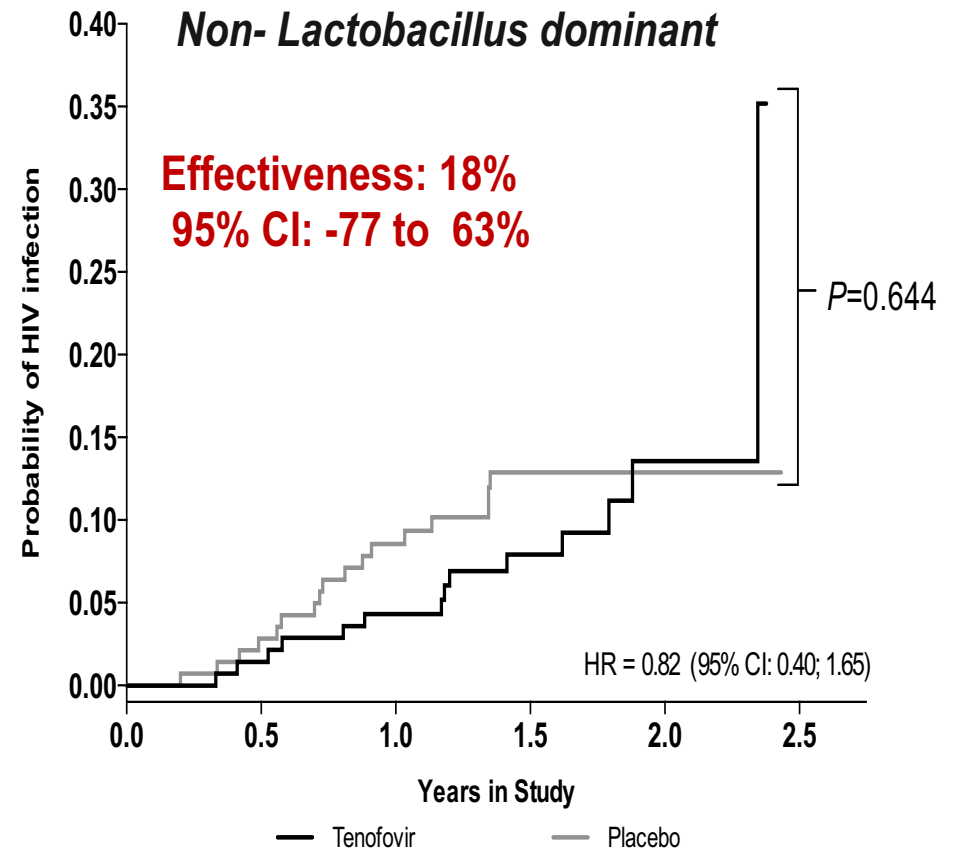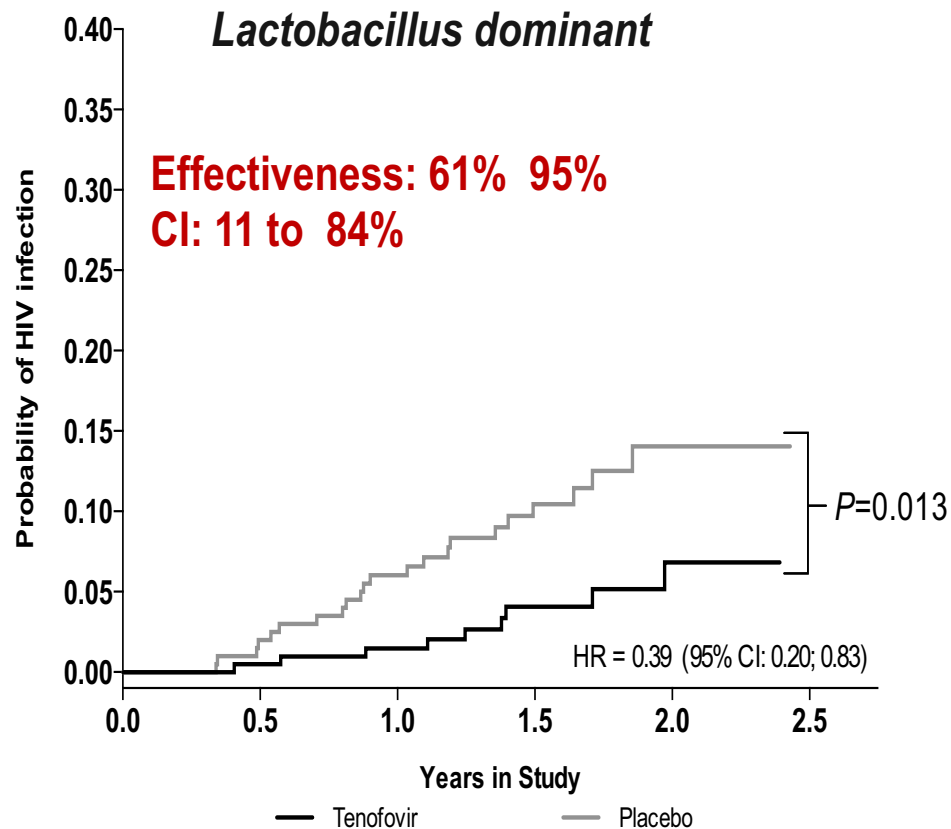
Tenofovir rapidly depleted by *Gardnerella* but not by *Lactobacillus*

Tenofovir (supernatant)

Legend:
- ▲ Abiotic
- ■ L. iners
- ● G. vaginalis

14.0%

67.4%
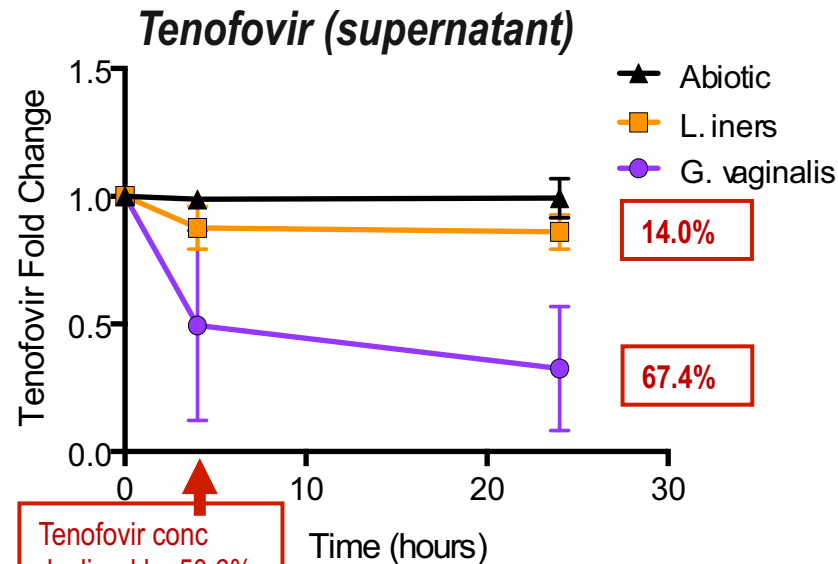
Tenofovir conc declined by 50.6% within 4 hrs

4 hours:
G. vag vs. L. iners: $P=0.002$
G. vag vs Abiotic: $P=0.005$

24 hours:
G. vag vs. L. ine s: $P<0.001$
G. vag vs Abiotic: $P<0.001$

Tenofovir (intracellular)

Legend:
- ■ L. iners
- ● G. vaginalis

Intracellular accumulation
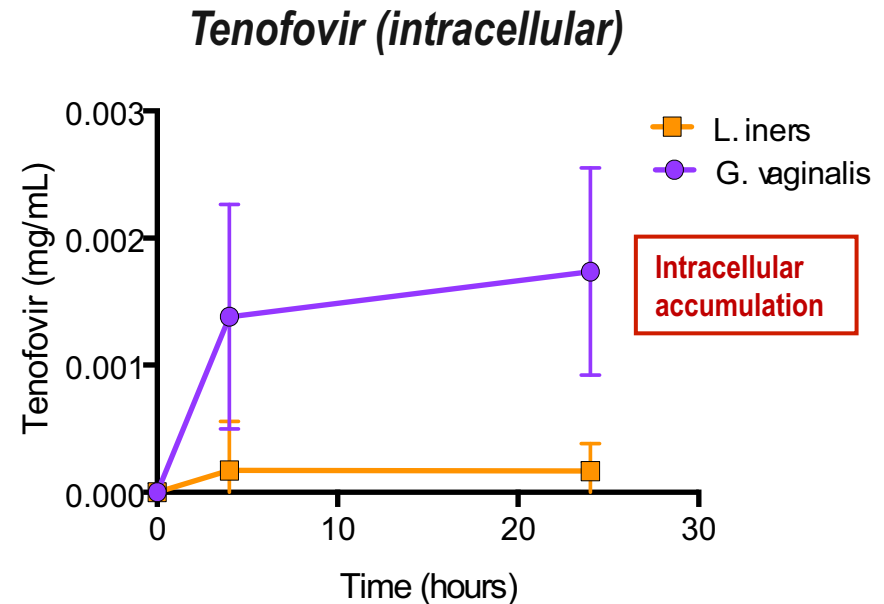
4 hours:
G. vag vs. L. iners: $P<0.001$

24 hours:
G. vag vs. L. iners: $P<0.001$

Bio-degradation of tenofovir by *Gardnerella*

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Conclusion

- **Unprecedented high burden of HIV in young women**

- **Greater understanding of WHY young women are at high risk**

- **Strong empiric evidence on**
  - Age disparate partnerships
  - Genital inflammation
  - *Prevotella bivia*
  - Absence of *Lactobacilli*
  - *Gardnerella vaginalis* compromises the activity of tenofovir
- **Implications for the design and testing of biomedical interventions**

- **Focussed effort to include young women who would benefit the most**

- **Ethical and programmatic challenges**

But need to pursue

Acknowledgements