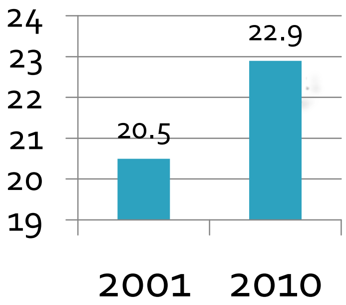
VLAD NOVITSKY

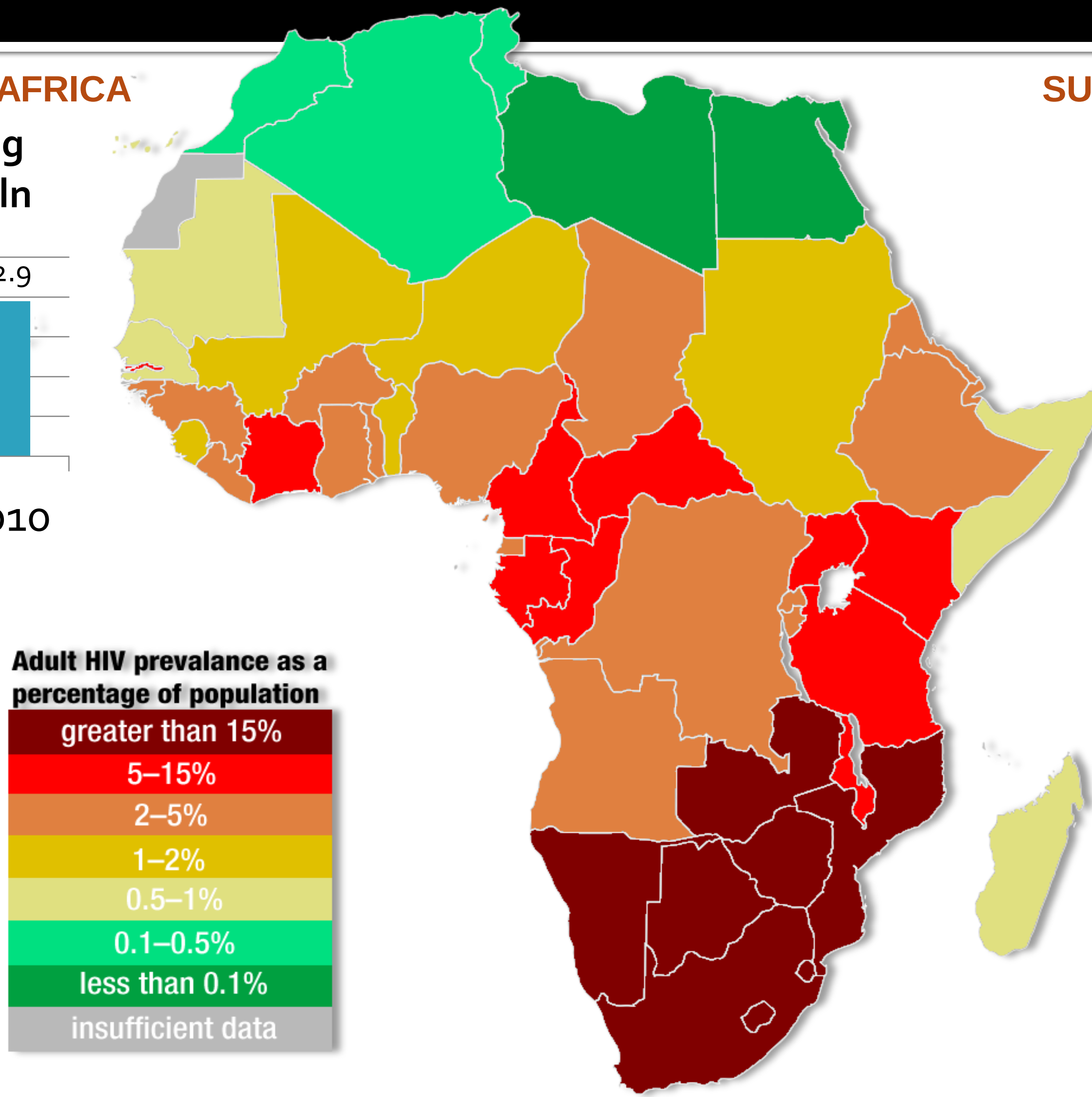
HIV-1 Viral Load and Viral Linkage in Treatment-as-Prevention Studies

HIV-1 Prevalence in Africa

SUB-SAHARAN AFRICA

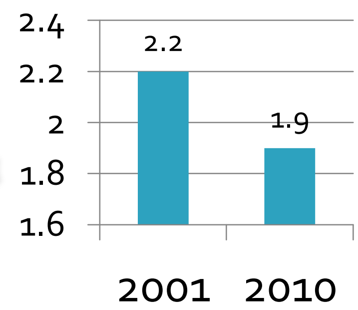
People living with HIV, mln



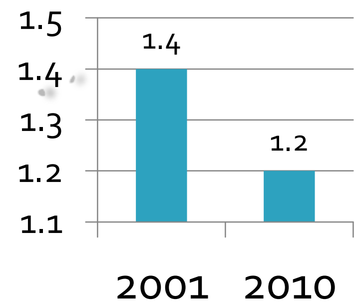


SUB-SAHARAN AFRICA

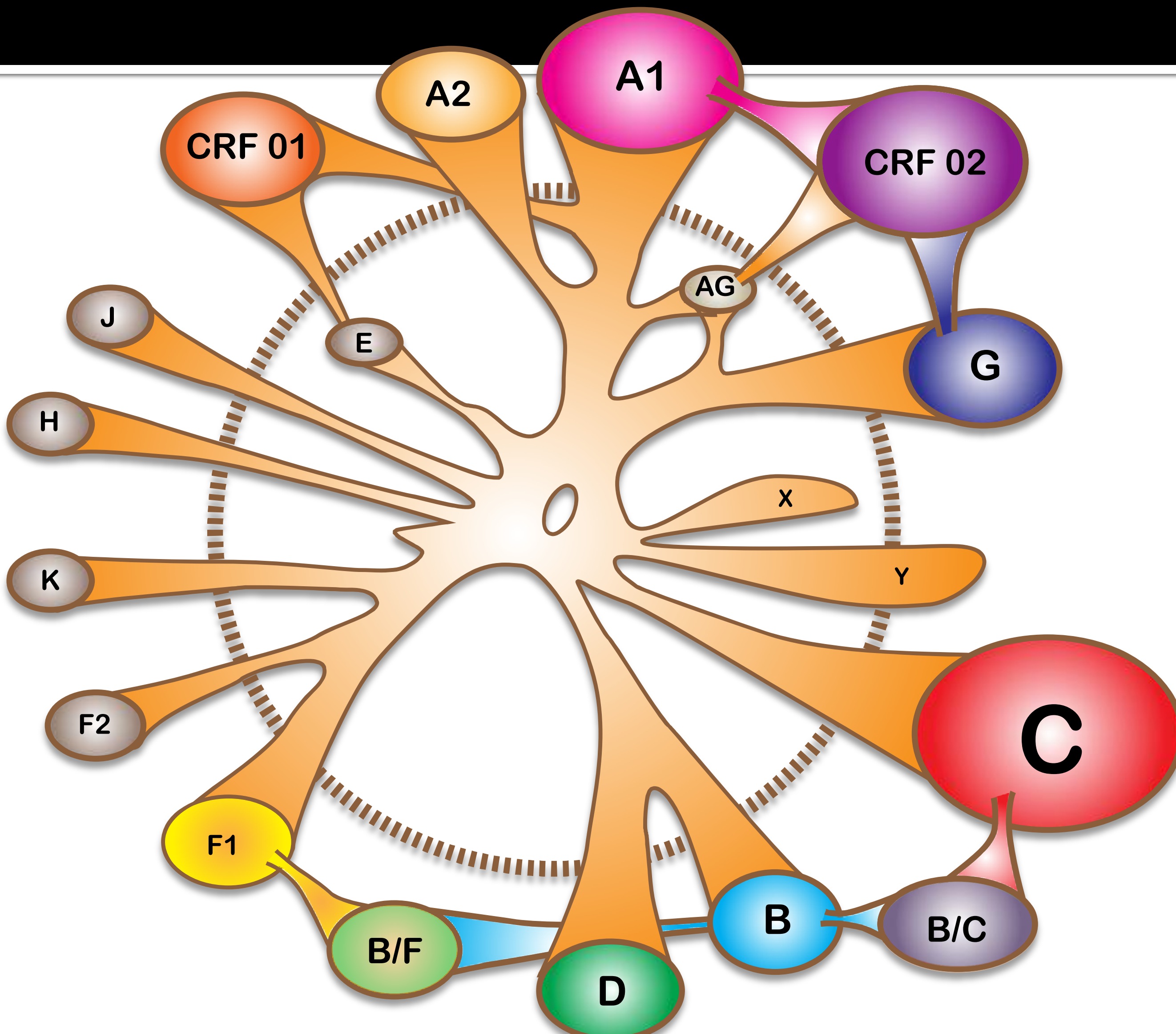
New HIV infections, mln



Death due to AIDS, mln



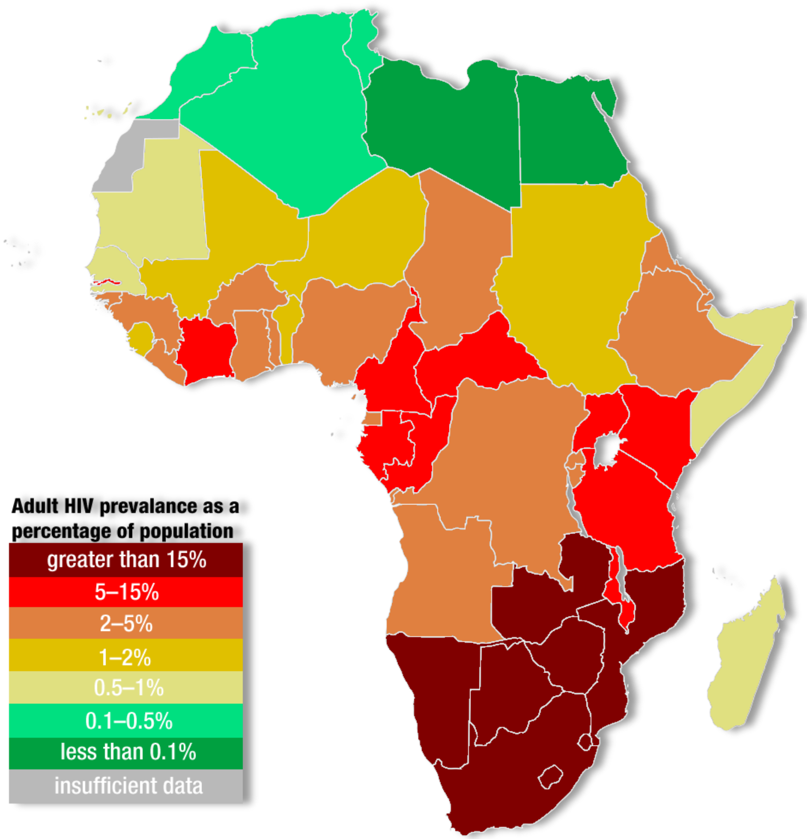
HIV-1 Subtypes: Current Epidemic



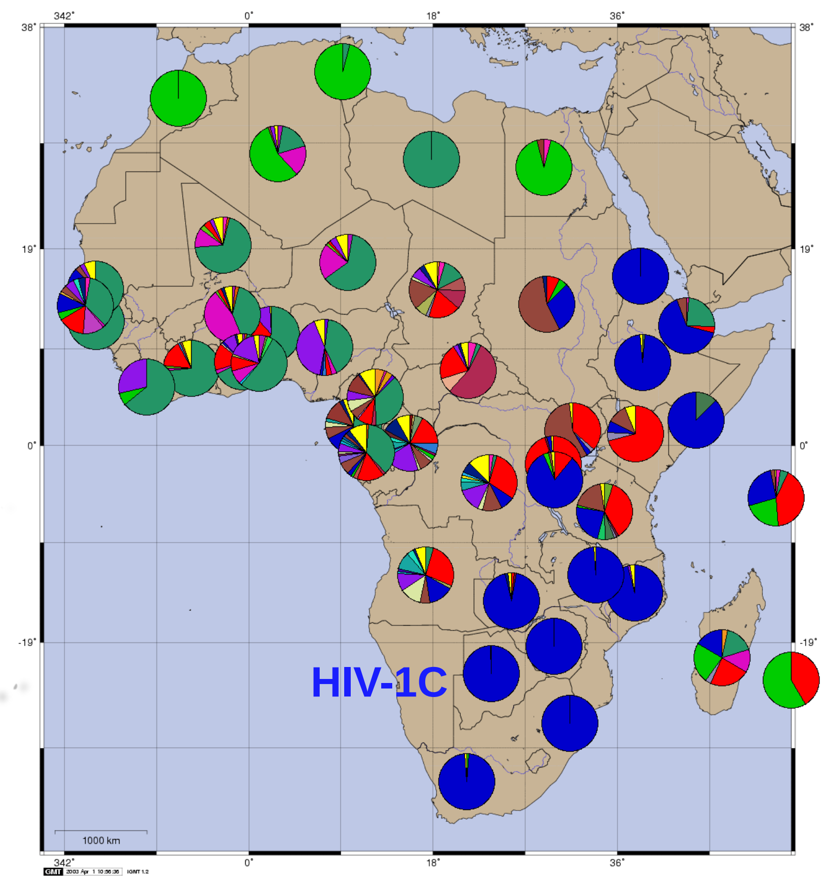
Adapted from: Zhang et al. 2010 *Retrovirology* 7:25

HIV-1 in Africa

HIV-1 Prevalence



HIV-1 Subtypes



Viral Linkage & Viral Load in TasP

ART for HIV-1 Prevention

- HIV-negative individuals:
  Pre- & Post-Exposure Prophylaxis
- HIV-positive individuals:
  Treatment as Prevention (TasP)

Viral Linkage & Viral Load in TasP

- **HIV-1 RNA load** is a marker of viral transmission. ART suppresses HIV replication.
- **High viremics**: a subset of HIV-infected individuals with high HIV-1 RNA load.
- **HIV-1 genotyping in TasP**:
  - Viral linkage: linked vs. unlinked cases;
  - High viremics disproportionally contribute to HIV incidence;
  - Extent of mixing between communities.

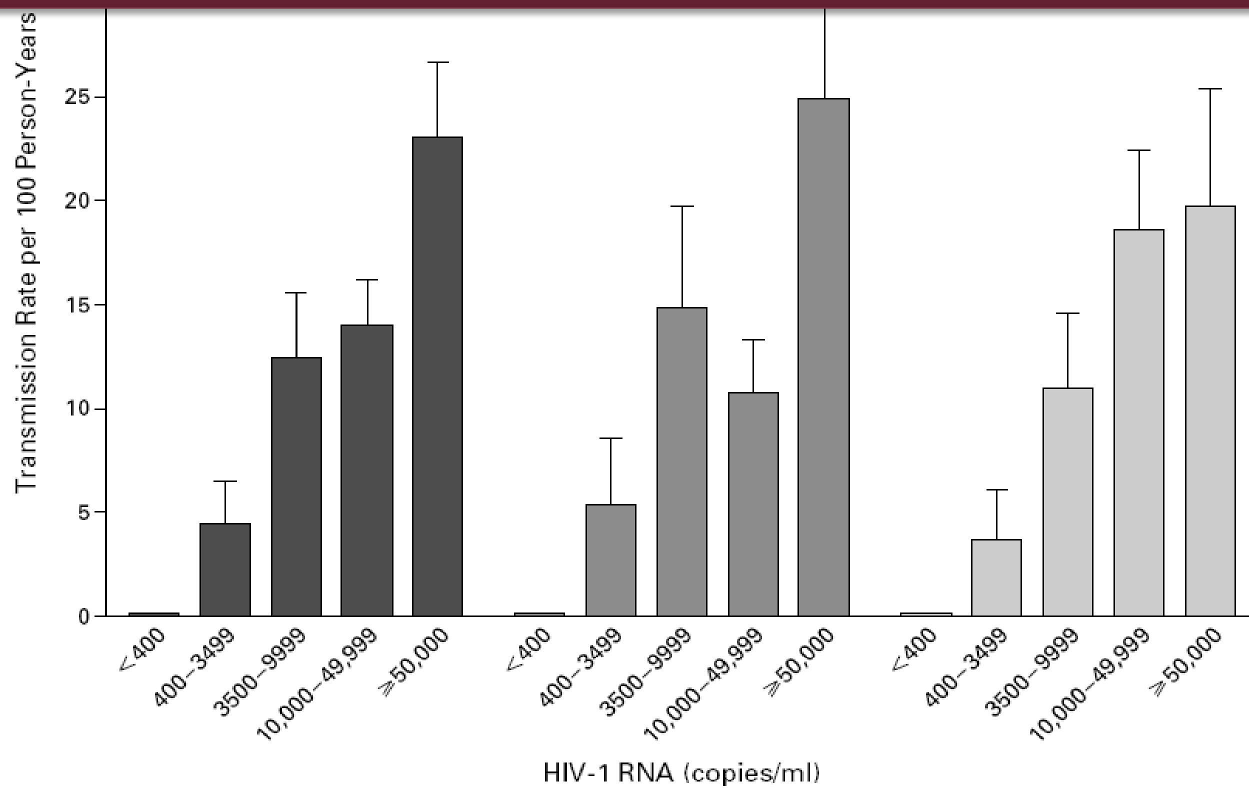
VIRAL LOAD AND HETEROSEXUAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

THOMAS C. QUINN, M.D., MARIA J. WAWER, M.D., NELSON SEWANKAMBO, M.B., DAVID SERWADDA, M.B., CHUANJUN LI, M.D., FRED WABWIRE-MANGEN, PH.D., MARY O. MEEHAN, B.S., THOMAS LUTALO, M.A., AND RONALD H. GRAY, M.D., FOR THE RAKAI PROJECT STUDY GROUP

NEJM, 2000

Viral load is the chief predictor of the risk of heterosexual transmission of HIV-1.

Transmission is rare if viral RNA levels are lower than 1,500 copies/ml.



The NEW ENGLAND JOURNAL of MEDICINE

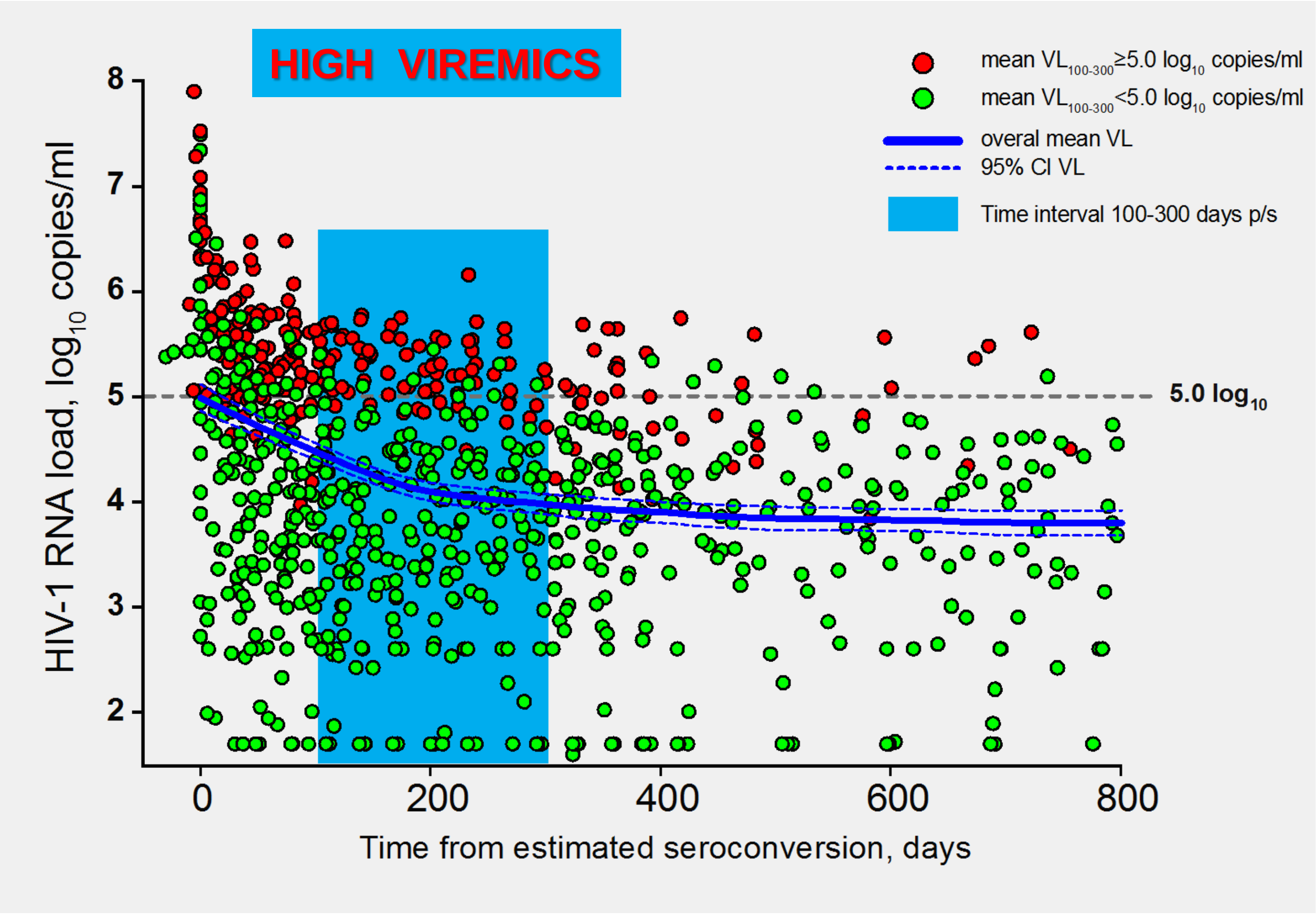
ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

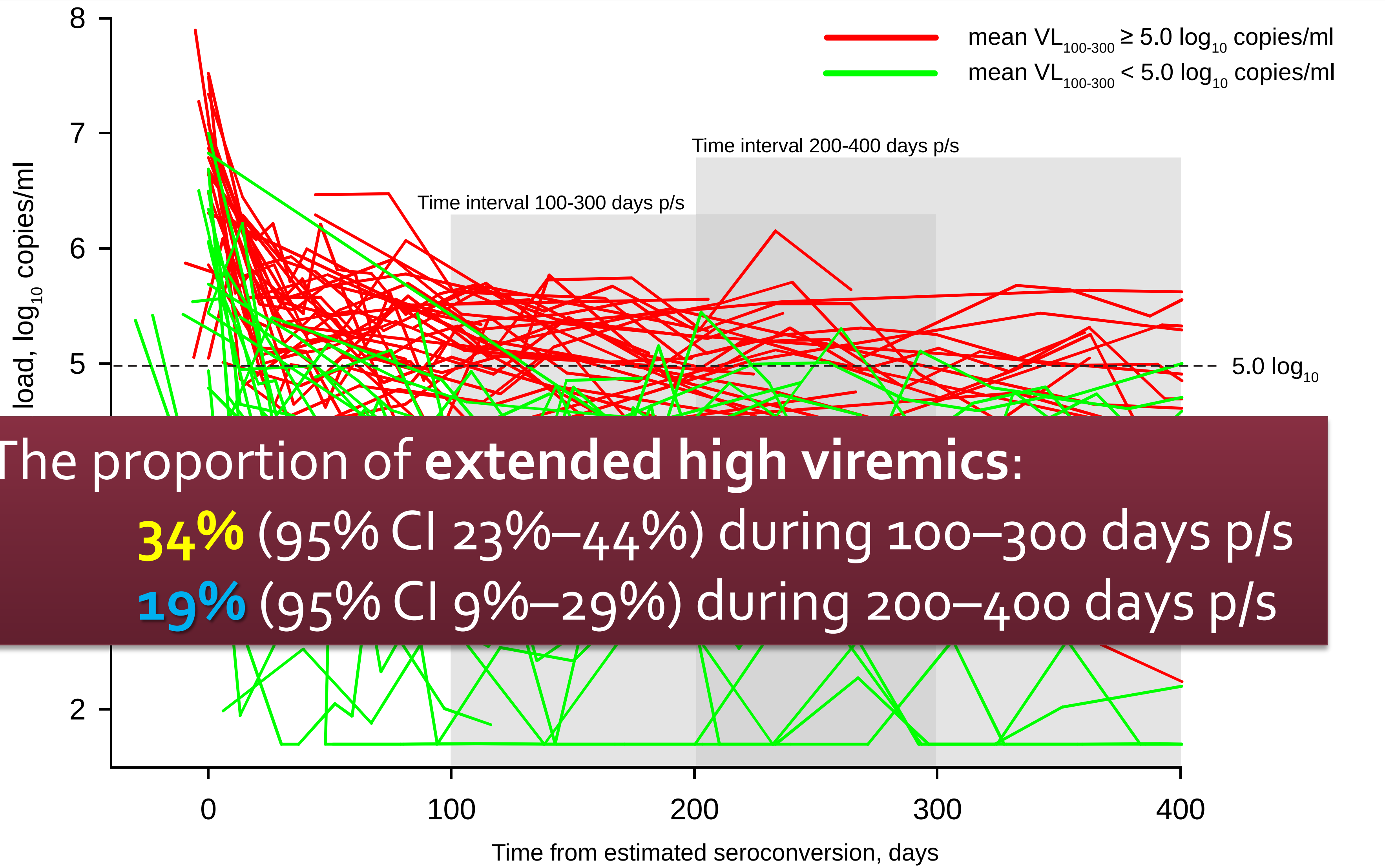
- **39** HIV-1 transmissions were observed
  - **11** unlinked
  - **28** linked to the infected partner
    - Immediate ART: **1** HIV transmission
    - Deferred ART: **27** HIV transmissions

96% reduction of HIV transmission due to early ART

HIV-1 RNA load in primary HIV-1C (pre-ART)



HIV-1 RNA load in primary HIV-1C (pre-ART)

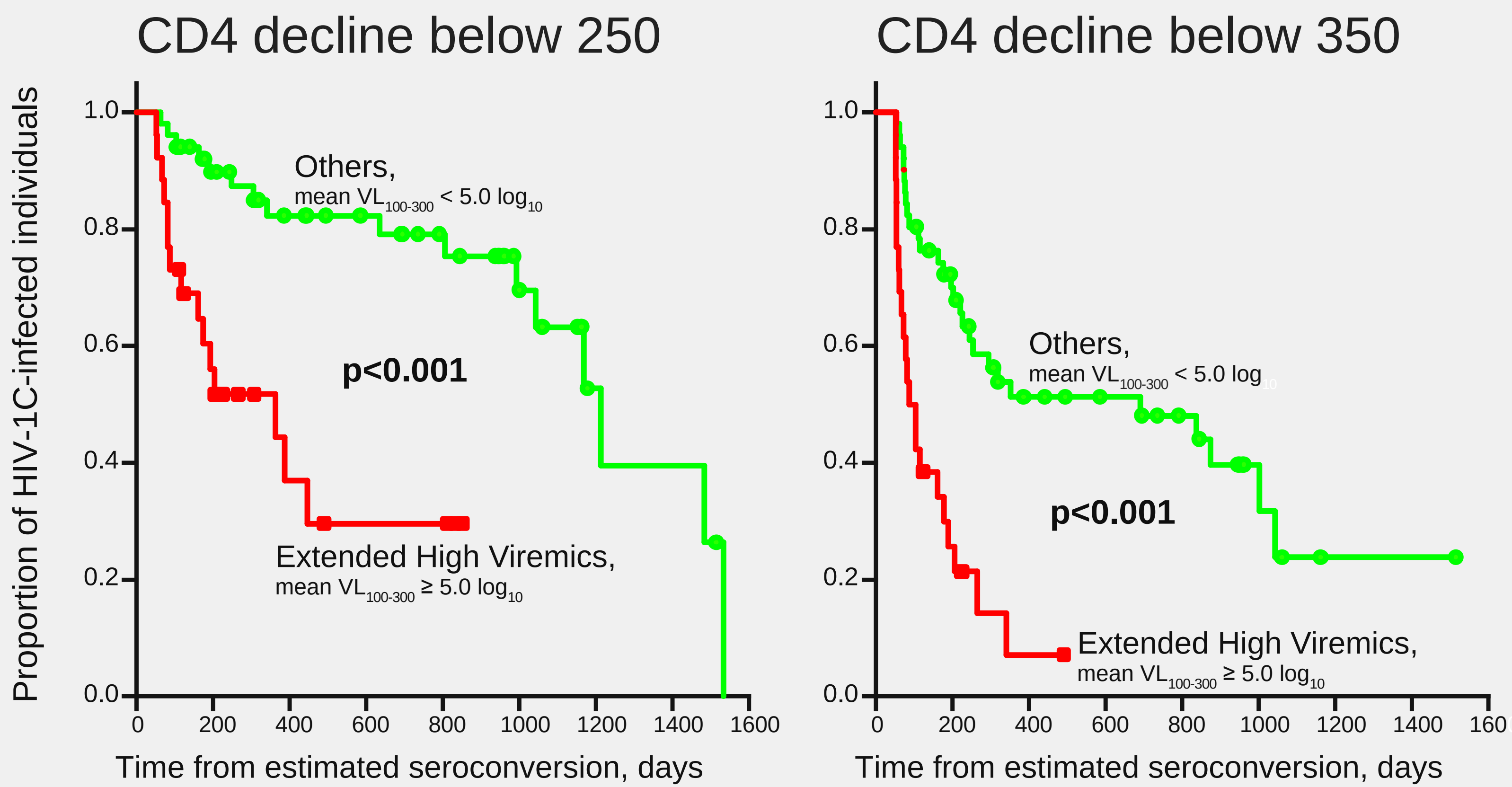


The proportion of **extended high viremics**:

34% (95% CI 23%–44%) during 100–300 days p/s

19% (95% CI 9%–29%) during 200–400 days p/s

Rapid decline of CD4+ T cells



Others:	51	39	30	26	21	12	4	3	51	31	19	16	12	5	1	1
Ext. High Viremics:	26	13	5	3	3	0	0	0	26	6	1	1	1	1	1	1

OPEN ACCESS Freely available online PLoS one

HIV-1 Subtype C-Infected Individuals Maintaining High Viral Load as Potential Targets for the "Test-and-Treat" Approach to Reduce HIV Transmission

Vladimir Novitsky[1,2], Rui Wang[3], Hermann Bussmann[1,2], Shahin Lockman[1,2], Marianna Baum[4], Roger Shapiro[1,2], Ibou Thior[1,2], Carolyn Wester[1,2], C. William Wester[1,2,7], Anthony Ogwu[1,2], Aida Asmelash[1,2], Rosemary Musonda[1,2], Adriana Campa[4], Sikhulile Moyo[2], Erik van Widenfelt[2], Madisa Mine[2], Claire Moffat[1,2], Mompati Mmalane[2], Joseph Makhema[1,2], Richard Marlink[1,2], Peter Gilbert[5], George R. Seage, III[6], Victor DeGruttola[3], M. Essex[1,2*]

Extended high viremics: a substantial fraction of individuals maintain high plasma viral RNA levels after acute HIV-1 subtype C infection

Vladimir Novitsky[a,b], Thumbi Ndung'u[c,d], Rui Wang[a], Hermann Bussmann[a,b], Fundisiwe Chonco[c], Joseph Makhema[a,b], Victor De Gruttola[a], Bruce D. Walker[d,e,f] and M. Essex[a,b]

AIDS 2011, **25**:1515–1522

CURRENT OPINION

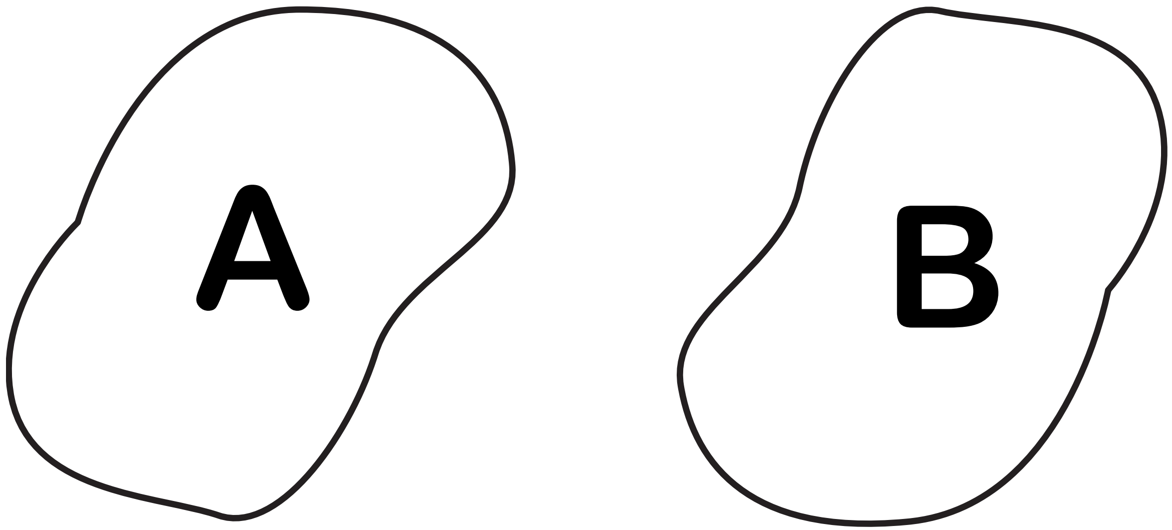
Using HIV viral load to guide treatment-for-prevention interventions

Curr Opin HIV AIDS 2012, 7:117–124

REVIEW

Vladimir Novitsky and Max Essex

HIV-1 Transmission: Viral Linkage

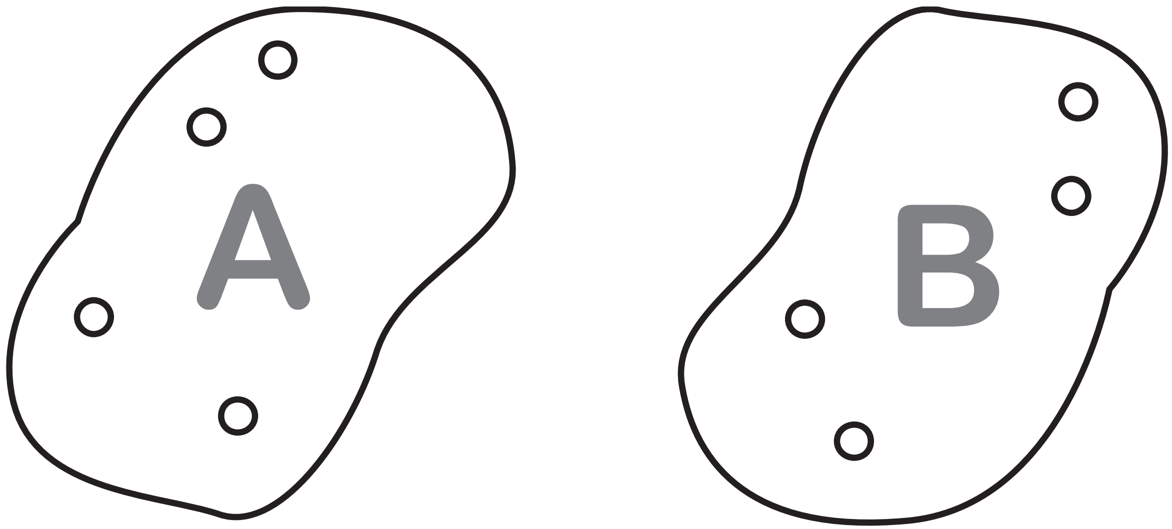


Control community

Intervention community

HIV-1 Transmission: Viral Linkage

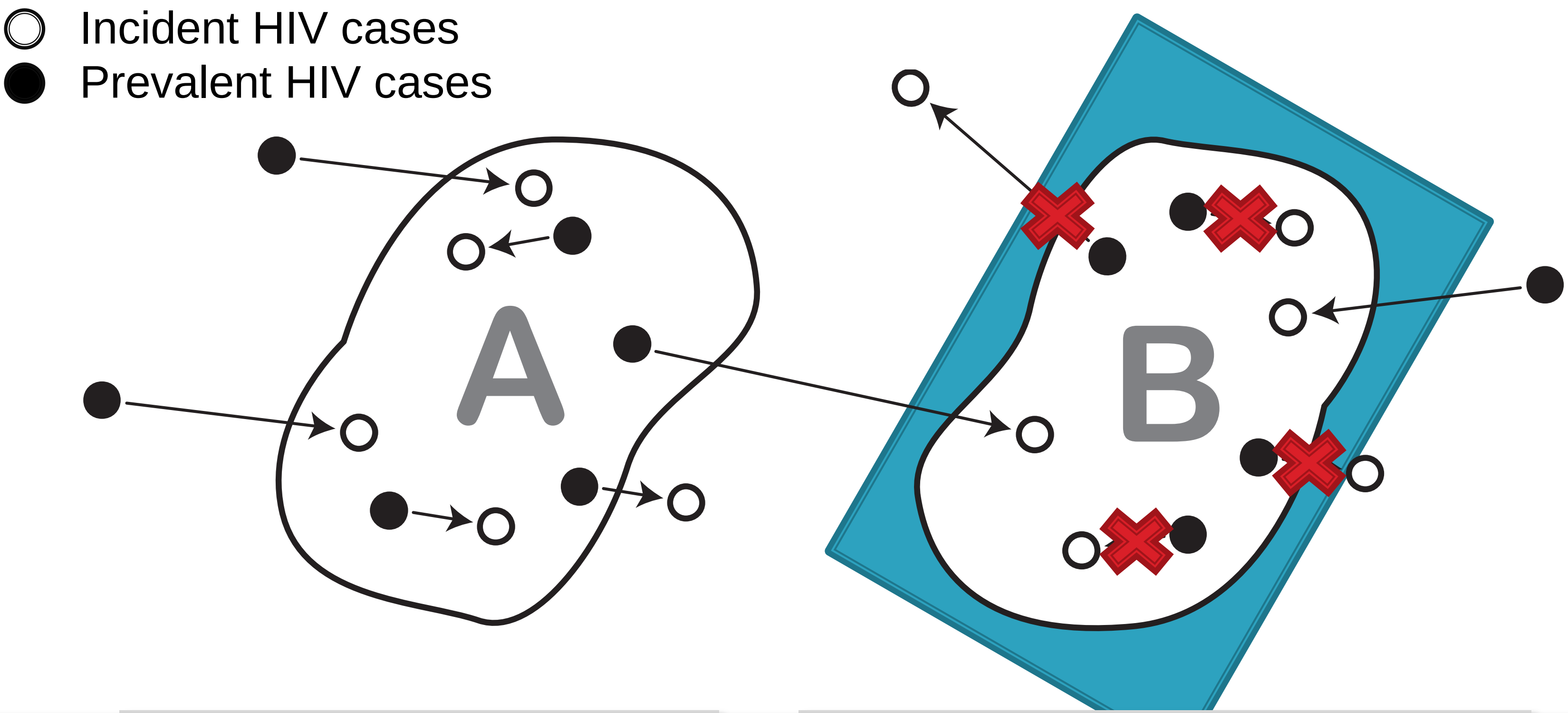
- Incident HIV cases



Control community

Intervention community

HIV-1 Transmission: Viral Linkage



Viral linkage:

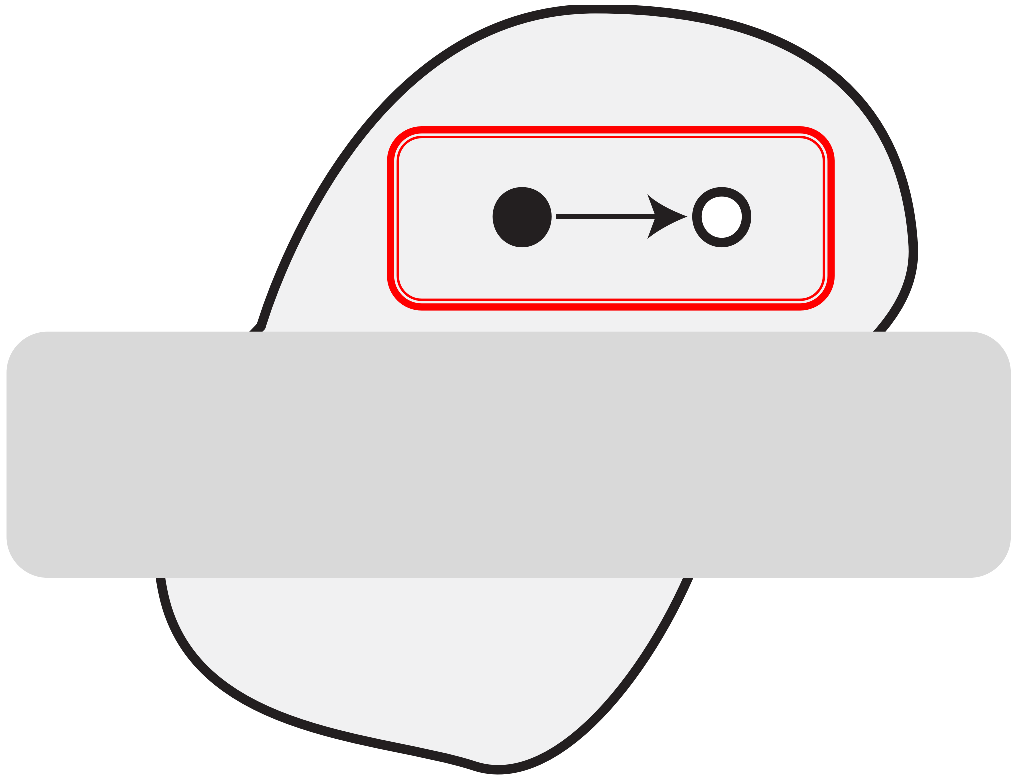
- To identify the source (within vs. outside) of HIV transmission
- **To refine estimates of HIV incidence**

HIV-1 Transmission: Viral Linkage

HIV Infections:

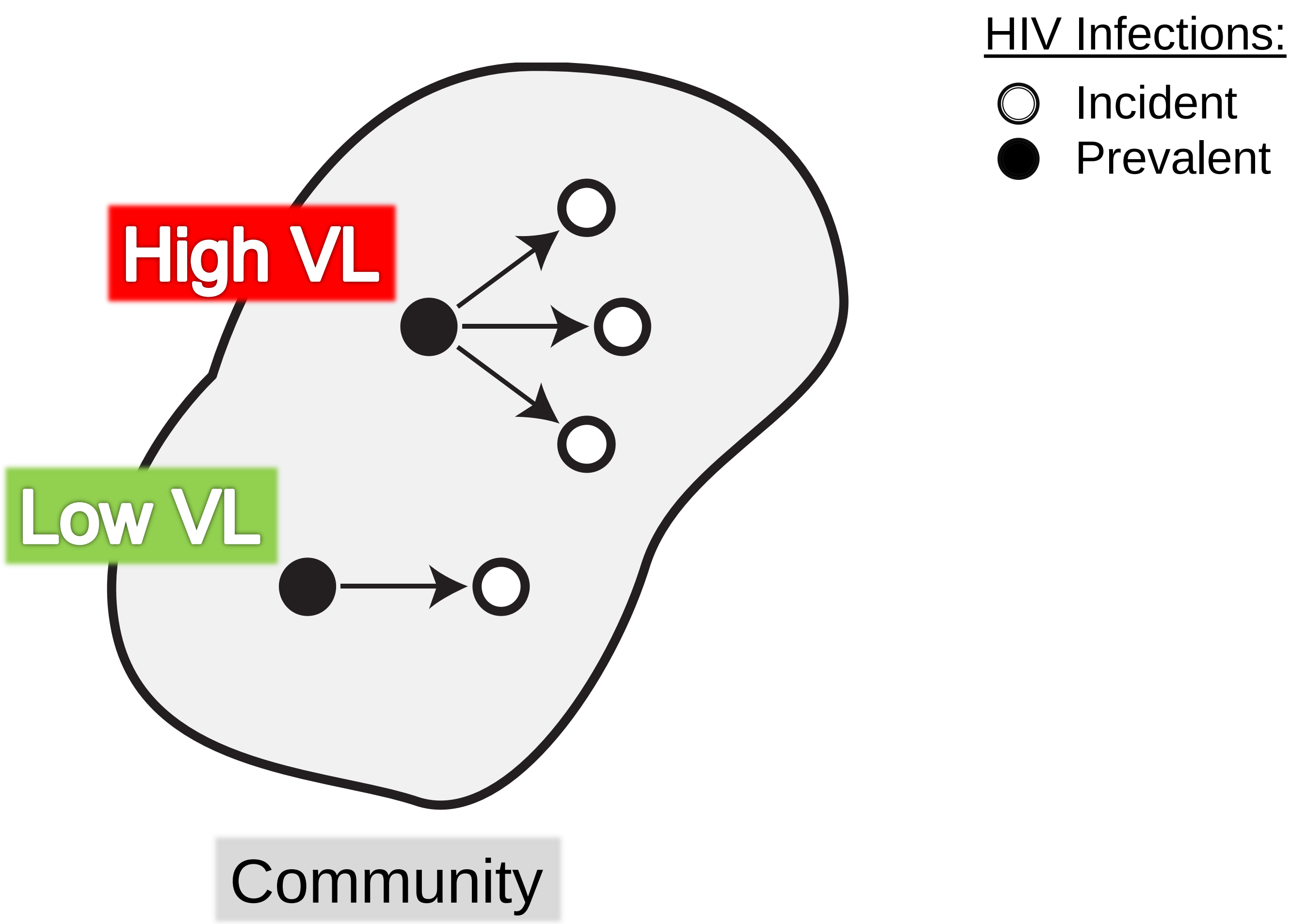
Incident

Prevalent

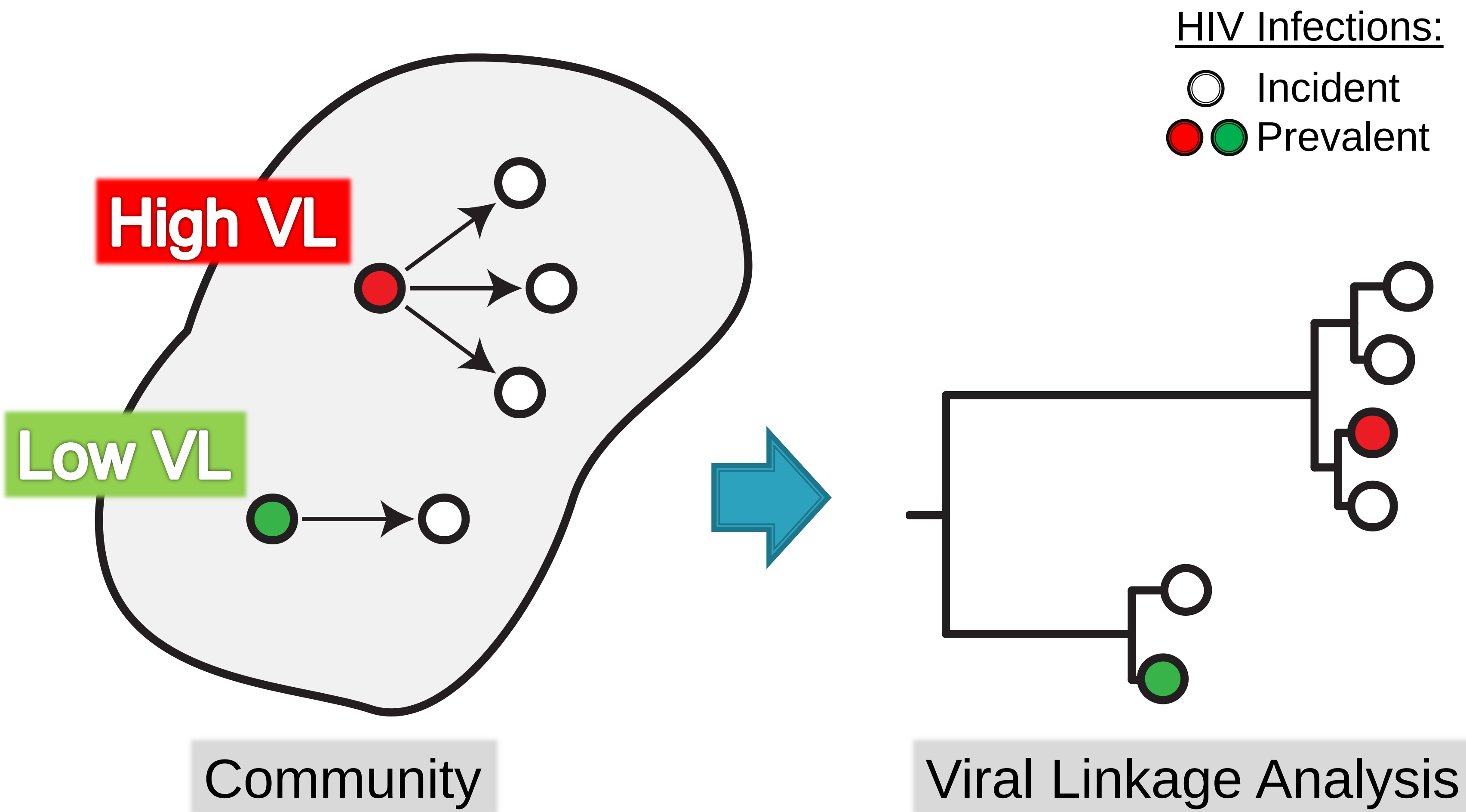


Community

HIV-1 Transmission: Viral Linkage



HIV-1 Transmission: Viral Linkage

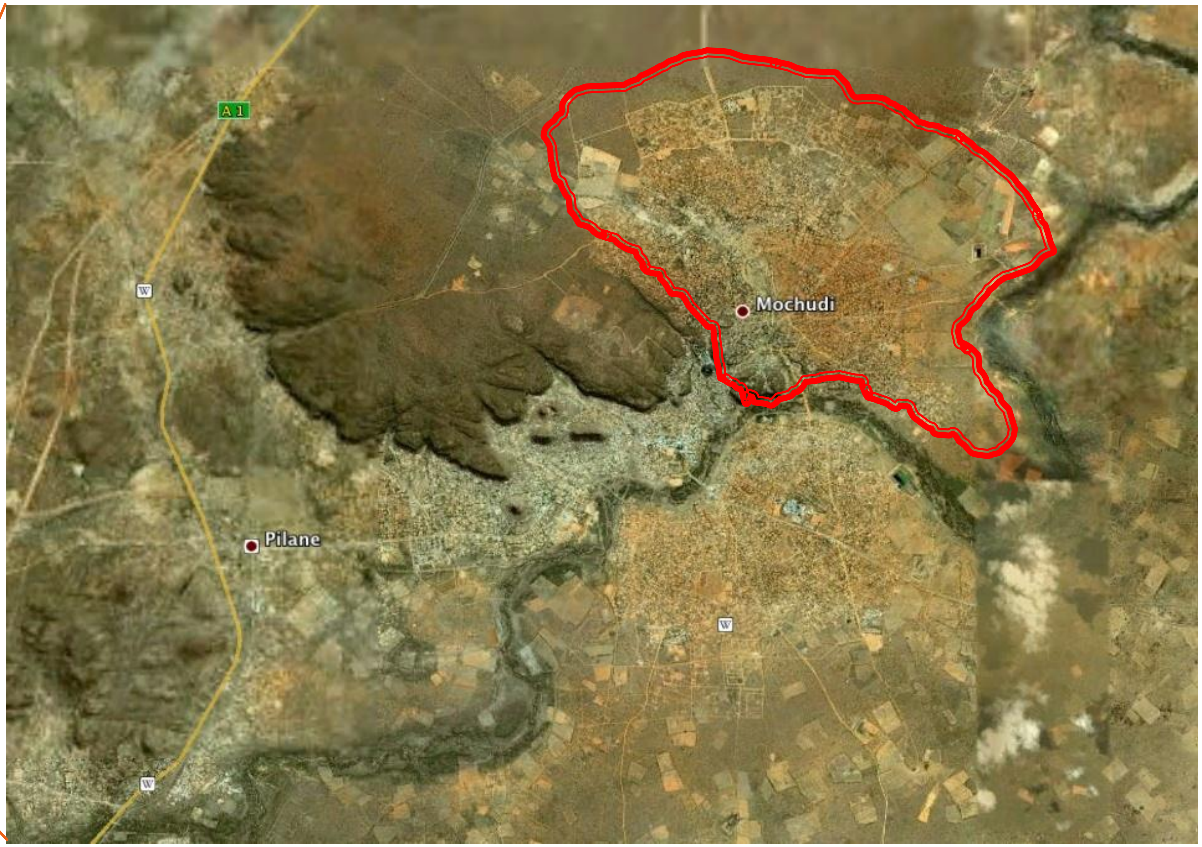


Mochudi Prevention Project, Botswana

- HIV-1 **incidence** and prevalence
- Social, educational, and behavioral risk factors
- Uptakes of VCT, condom use, and sMC
- Viral linkage and clustering (in relation to high viral load)
- Uptake of **ART as prevention** (VL ≥50,000)
- Develop mathematical models for control strategies

Mochudi Prevention Project

BOTSWANA



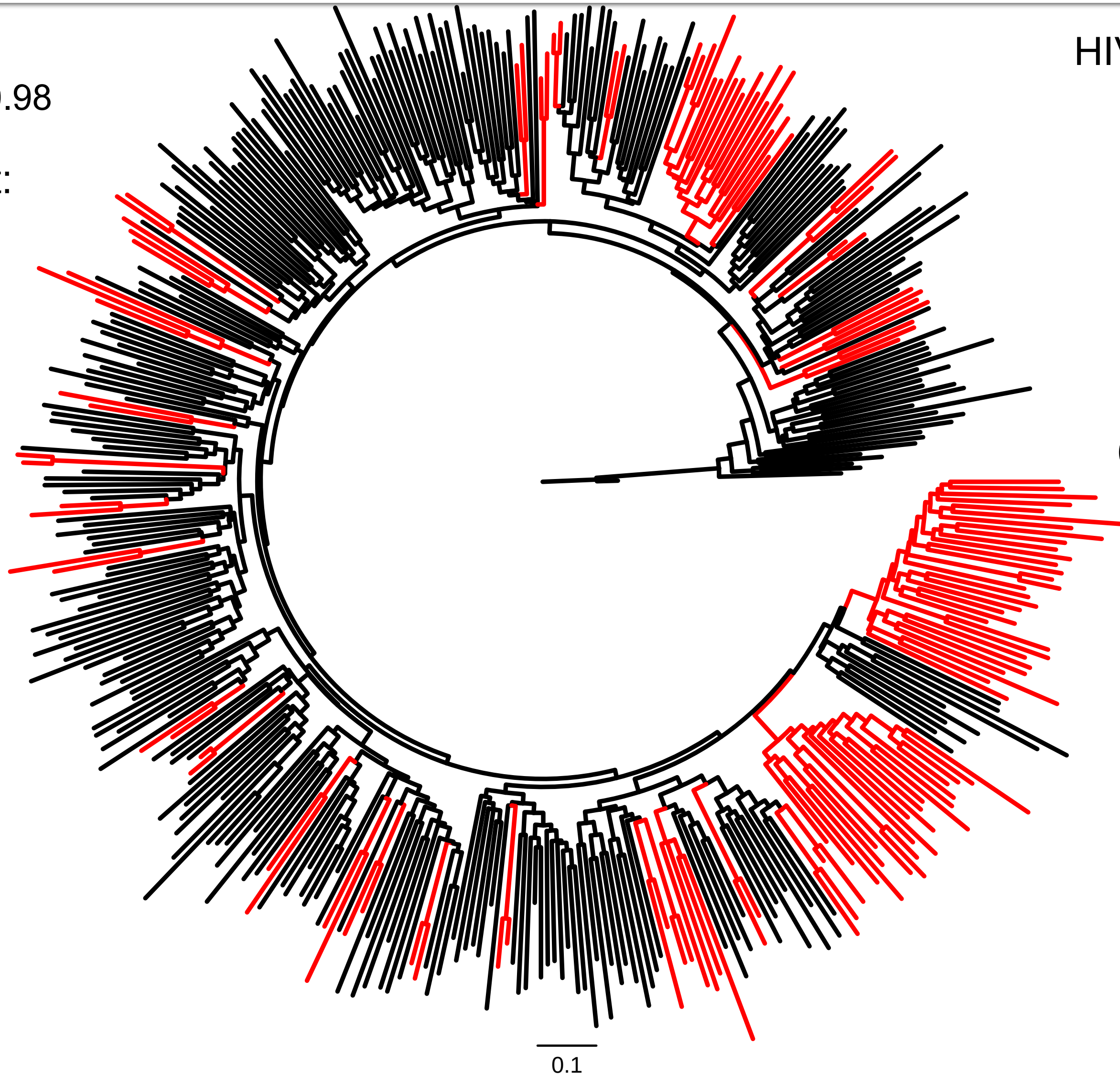
Mochudi: Large rural village, 44,000 people

Mochudi Project: Viral linkage

ML tree

aLRT≥0.98

jModelTest:
TrN+G+I
PhyML



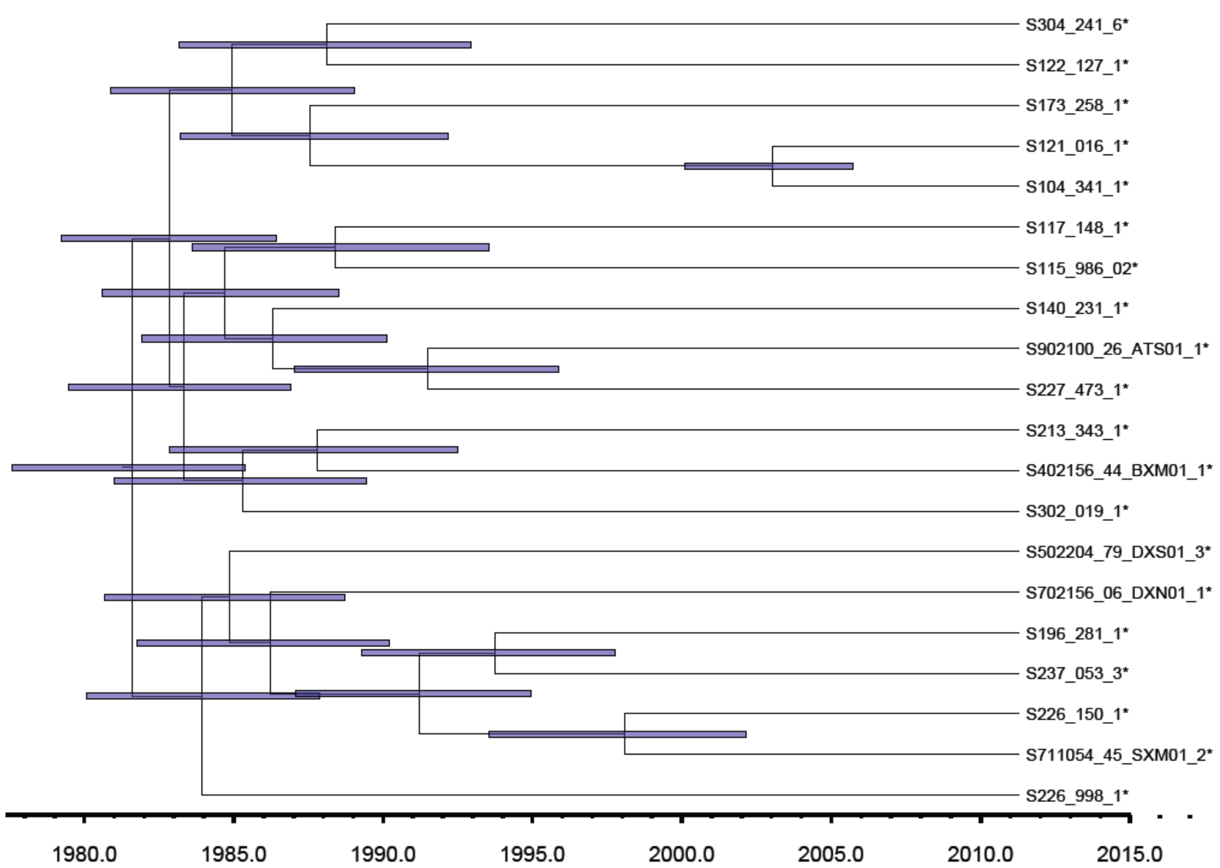
HIV-1C *env* sequences
431 individuals
(021M)

32 clusters:
33.9%
(146 of 431 sequences)

Seqs per cluster	Clusters, n
2	23
3	4
4	1
13	1
18	1
22	1
31	1

Mochudi Project: HIV-1C clusters

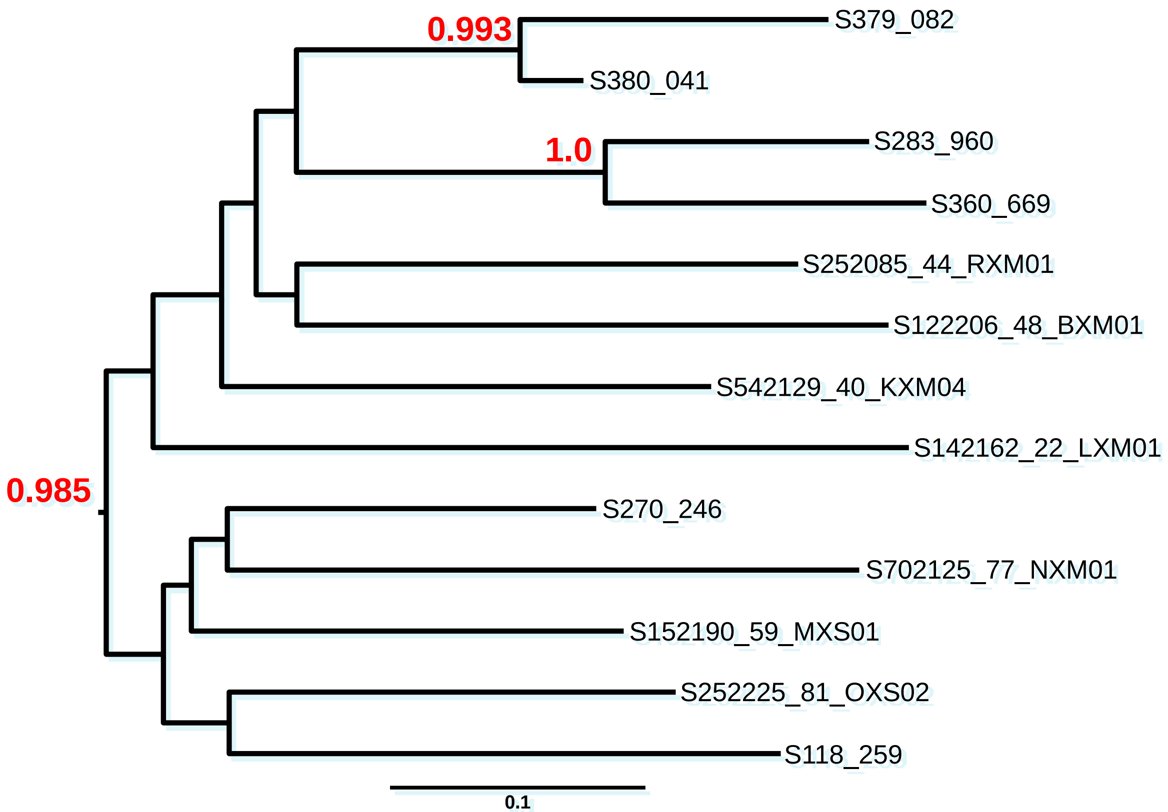
Cluster 02: 20 subjects (prevalent cases)



Method	Model	Reliability of the cluster
ML	PhyML jMT	0.983 (aLRT)
ML	FastTree 2, GTR+G	0.996 (Shimodaira-Hasegawa)
NJ	FastTree 2, noML	0.953 (Shimodaira-Hasegawa)
Bayesian	Mr. Bayes, GTR+G, 20M chain	0.999 (clade credibility value)

Mochudi Project: HIV-1C clusters

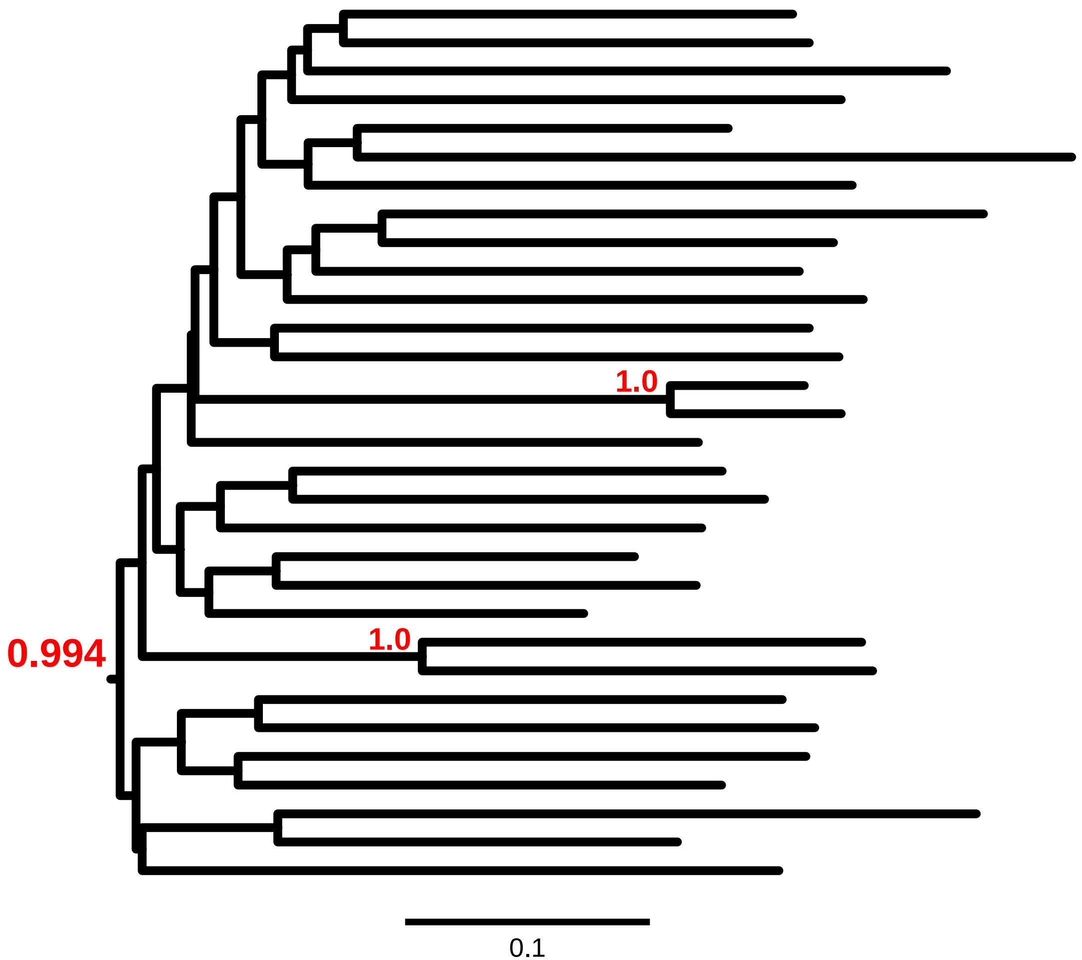
Cluster 13: 13 subjects (prevalent cases)



Method	Model	Reliability of the cluster
ML	PhyML jMT	**0.985** (aLRT)
ML	FastTree 2, GTR+G	**0.951** (Shimodaira-Hasegawa)
NJ	FastTree 2, noML	**0.988** (Shimodaira-Hasegawa)

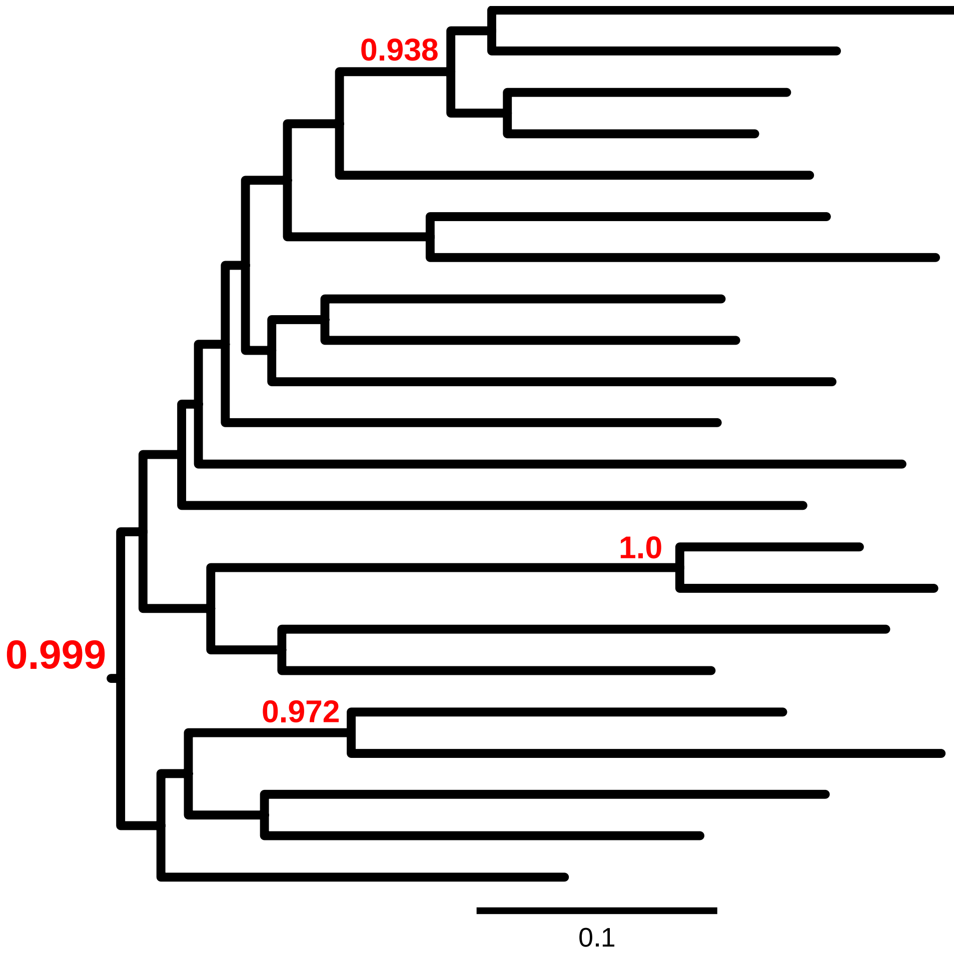
Mochudi Project: HIV-1C clusters

Cluster 15: 31 subjects (prevalent cases)



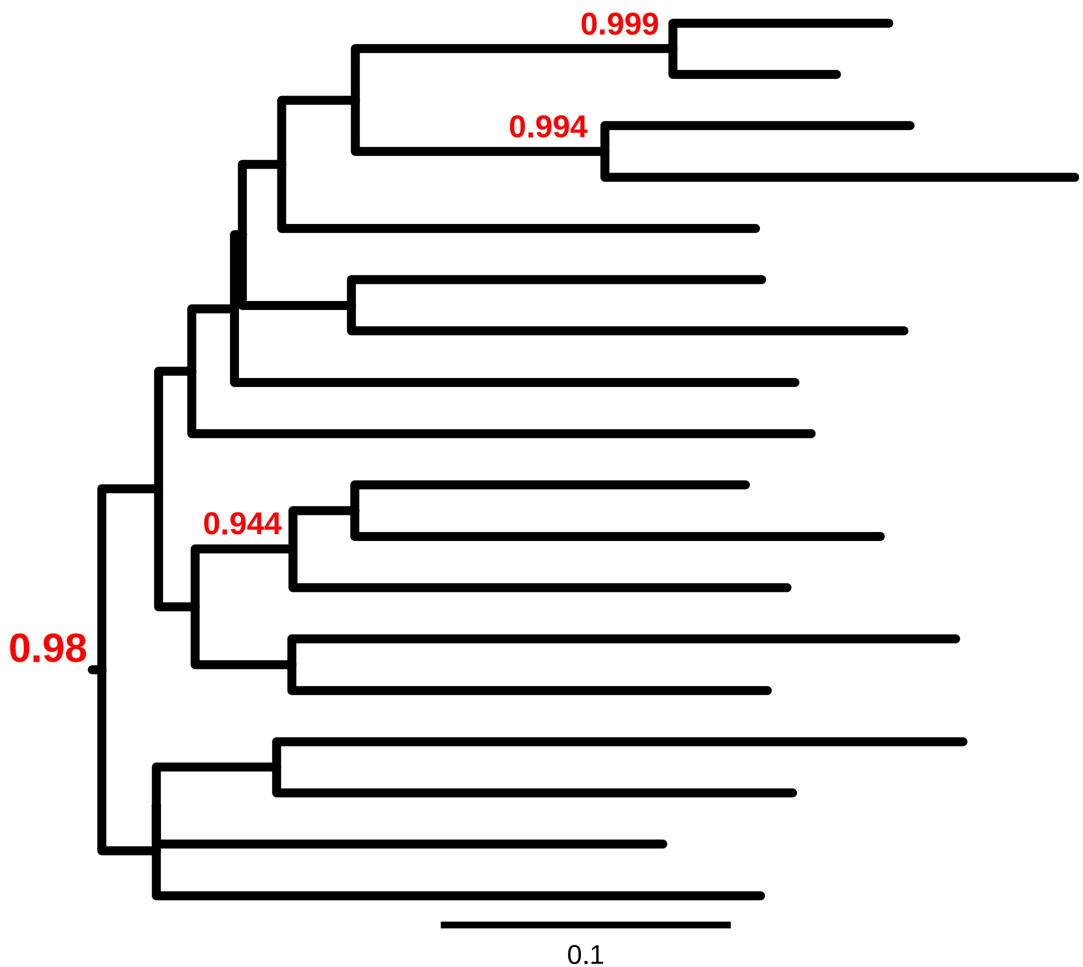
Mochudi Project: HIV-1C clusters

Cluster 16: 22 subjects (prevalent cases)

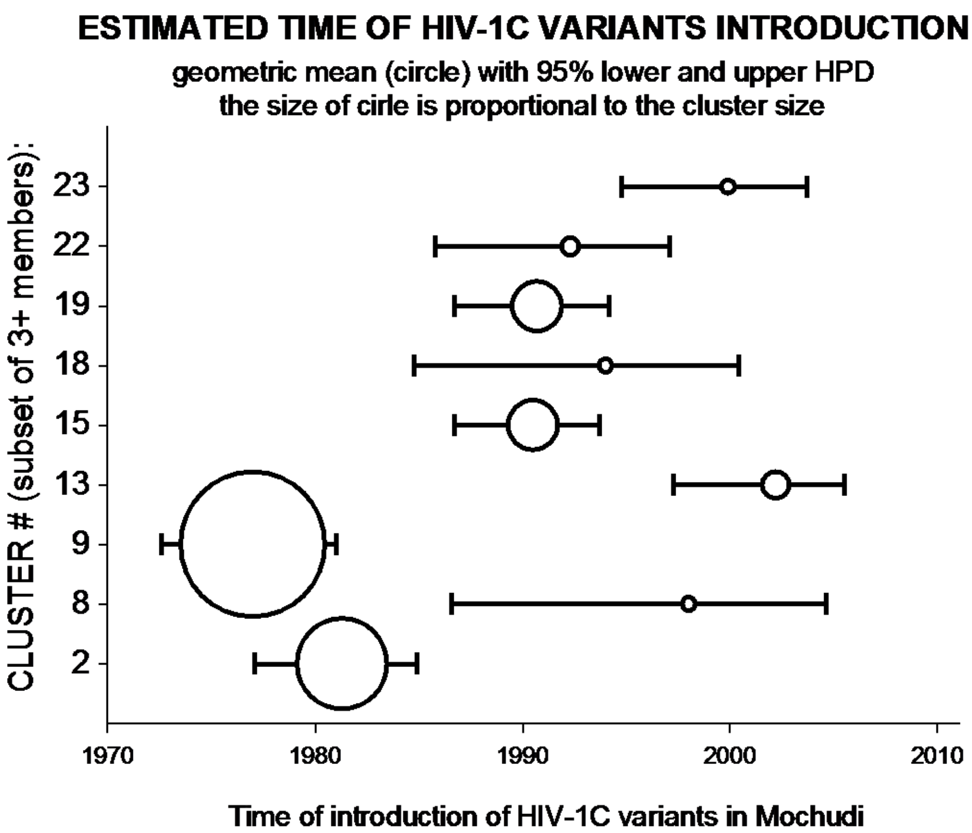


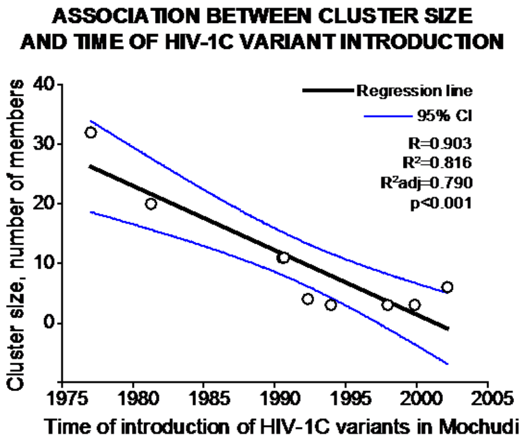
Mochudi Project: HIV-1C clusters

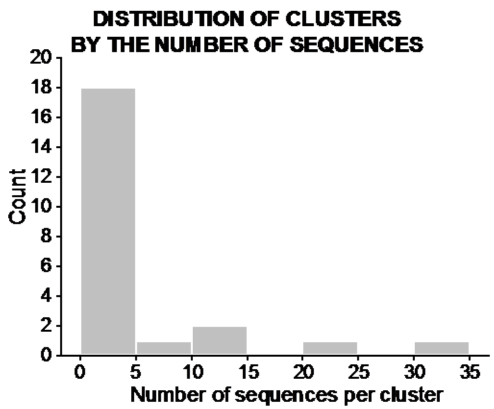
Cluster 25: 18 subjects (prevalent cases)



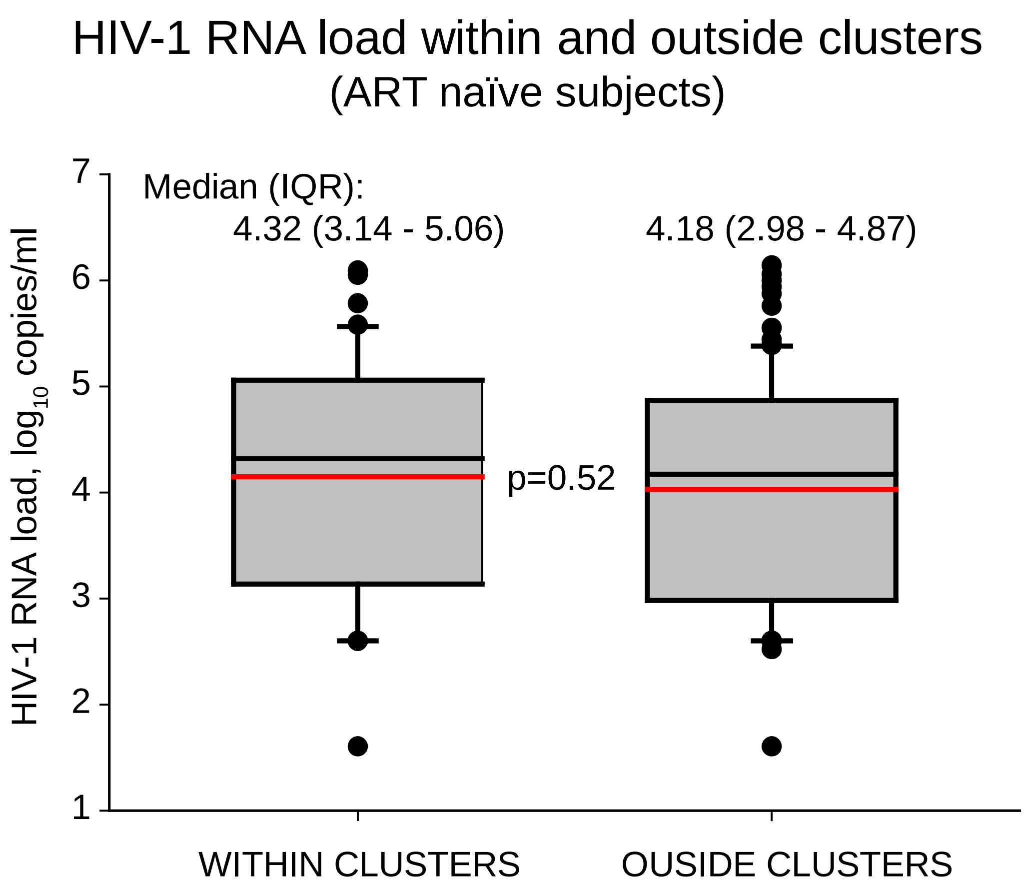
Mochudi Project: HIV-1C clusters

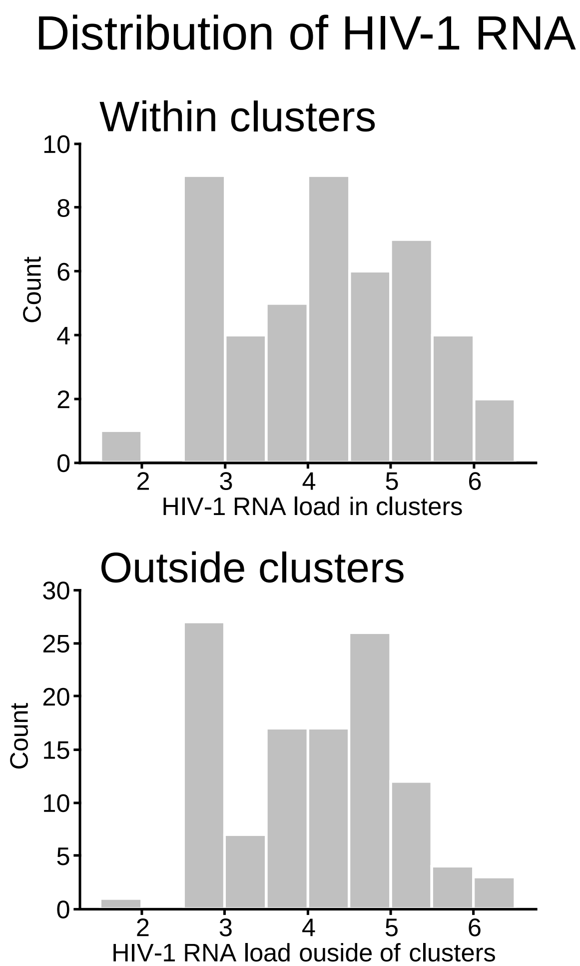




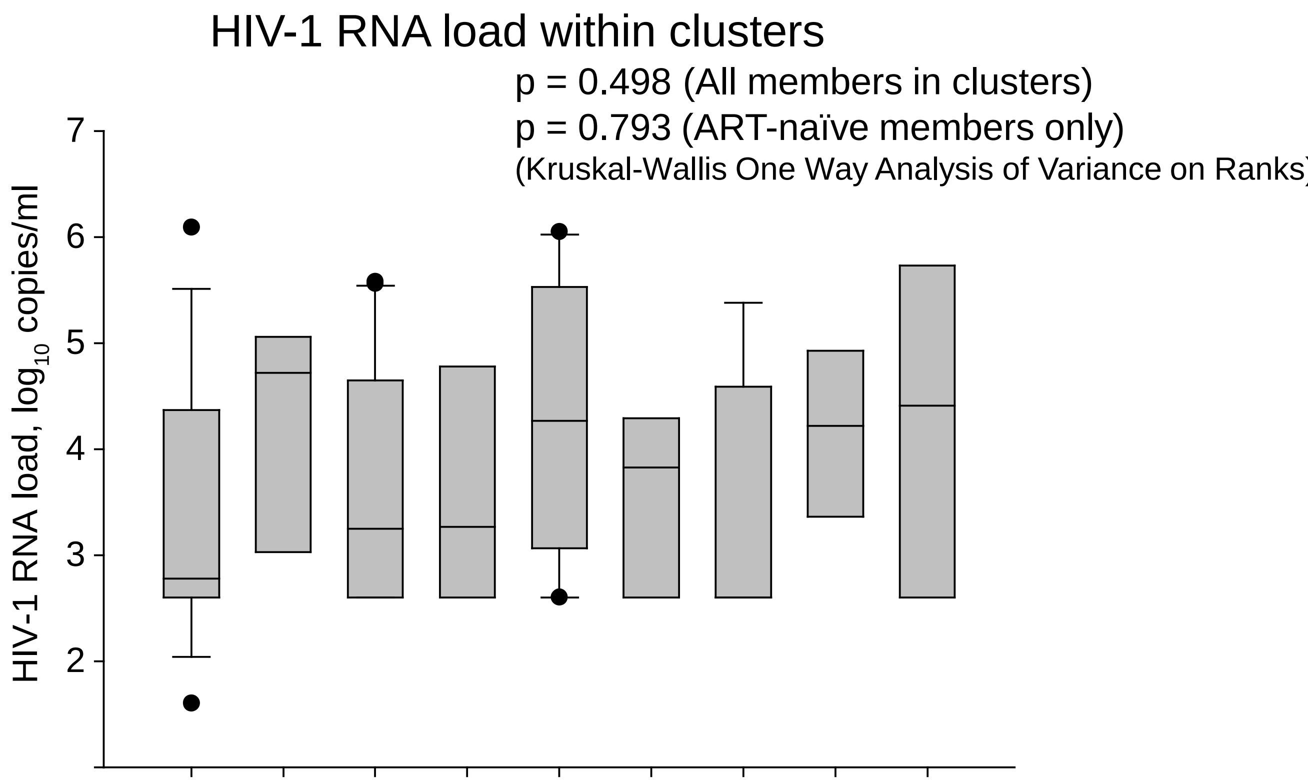


Mochudi Project: HIV-1C clusters





Mochudi Project: HIV-1C clusters



CLUSTER NUMBER:	2	8	9	13	15	18	19	22	23
MEMBERS, n:	20	3	32	6	11	3	11	4	3
PROPORTION ON ART, %:	18%	0	32%	25%	30%	33%	44%	0	67%

HTC & Linkage to Care: Screening Algorithm

- **HIV status**
  - RHT
    - If HIV+: CD4 test
- **CD4 test**
  - 350
    - If <350: ART
    - If >350: VL test
- **HIV-1 RNA load**
  - 10K
    - If >10K: ART
    - If <10K: Monitor

HTC & Linkage to Care: Screening Algorithm

HIV status → **CD4 test** → **HIV-1 RNA load**

- **RHT**
  - HIV+*: 21%
- **350**
  - <350: 47%
  - >350: 53%
- **10K**
  - >10K: 43%
  - <10K: 57%

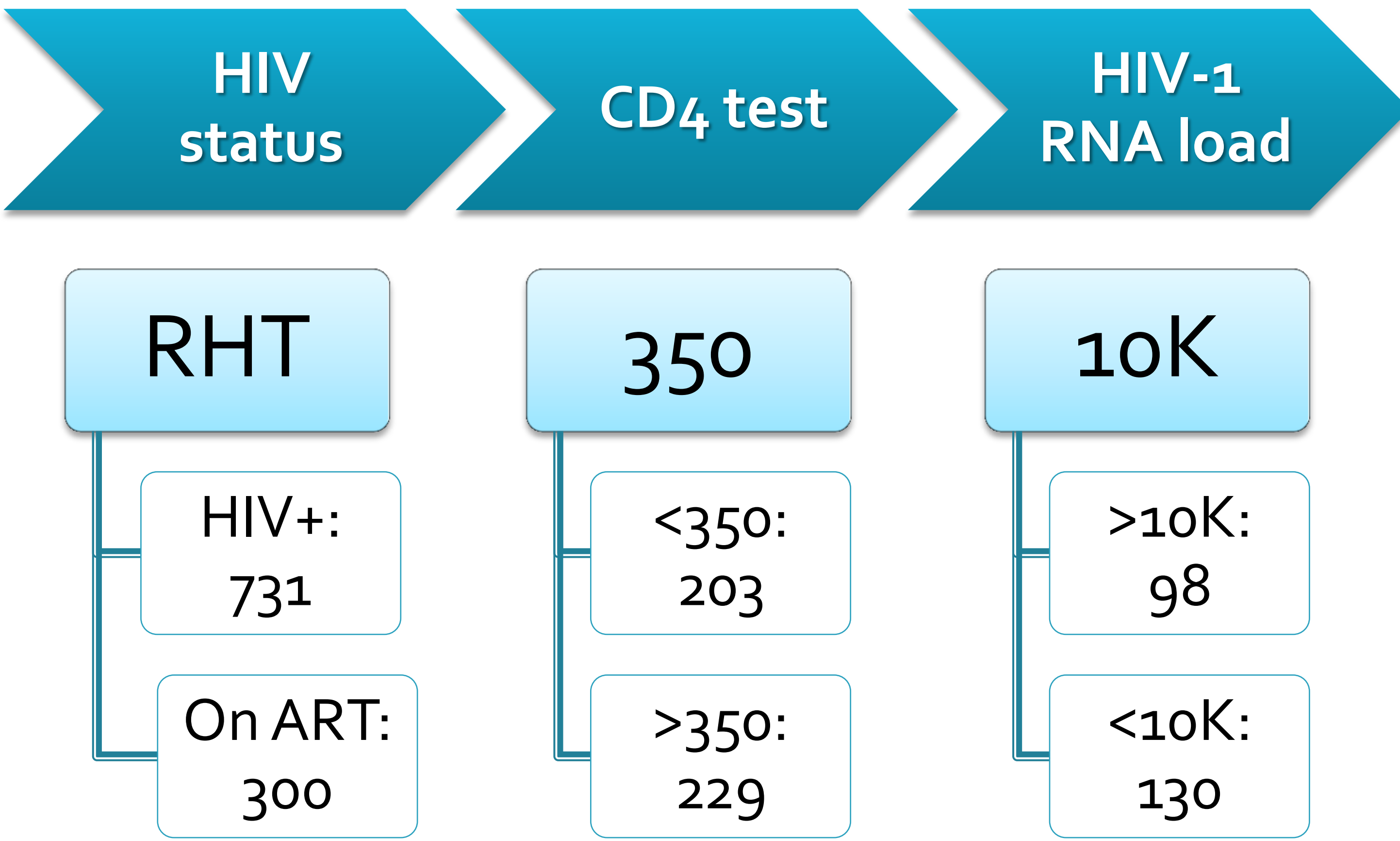
NNT:
Number
Needed
to Treat

* 41% of HIV-infected individuals are on ART

HTC & Linkage to Care: Screening Algorithm

HYPOTHETICAL EXAMPLE

Average community:
- total population ~6,000
- age eligible for HTC (16–64 y.o.) 3,480



NNT:
Number
Needed
to Treat

HTC & Linkage to Care: Screening Algorithm

HYPOTHETICAL EXAMPLE: ESTIMATED COST

Average community:
- total population ~6,000
- age eligible for HTC (16-64 y.o.) 3,480

POC CD4: $12 / test
Lab-based VL: $32 / test
ART cost, per year: $385

HIV status → **CD4 test** $12/POC test → **HIV-1 RNA load**

RHT
- HIV+: n=731
- On ART: n=300

CD4 cost: $5,174
- <350: n=203
- >350: n=229

VL cost: $7,313
- ART>10K: **$37,834**
- ART<10K: **$50,149**

Cost per year

HTC & Linkage to Care: Screening Algorithm

HYPOTHETICAL EXAMPLE: ESTIMATED COST COMPARISON

HIV-infected individuals with CD4 > 350:

VIRAL LOAD-DRIVEN TASP

- Total cost: $50,318
  - CD4 testing: $5,174
  - VL testing: $7,313
  - ART: $37,662
- Savings per year: $37,662
  - % Savings: 46%

UNIVERSAL TASP

- Total cost: $93,155
  - CD4 testing: $ 5,174
  - VL testing: $0
  - ART: $87,981
- Savings per year: $0
  - % Savings: 0

Treatment as Prevention

- **Botswana Combination Prevention Project (BCPP)**

Botswana Combination Prevention Project
PI: Max Essex

- Community-randomized TasP trial in Botswana.
- 30 communities, 15 pairs:
  - Arm A: control communities, standard-of-care, ART at CD4<350
  - Arm B: intervention communities.
- ART: in adults with high HIV-1 RNA load (>10K copies/ml) to prevent HIV transmissions.
- Viral linkage will used to estimate source of HIV infection.
- Targeted population (16-64 y.o.): ~100K.
- Duration of the study: 4 years.

Botswana Combination Prevention Project

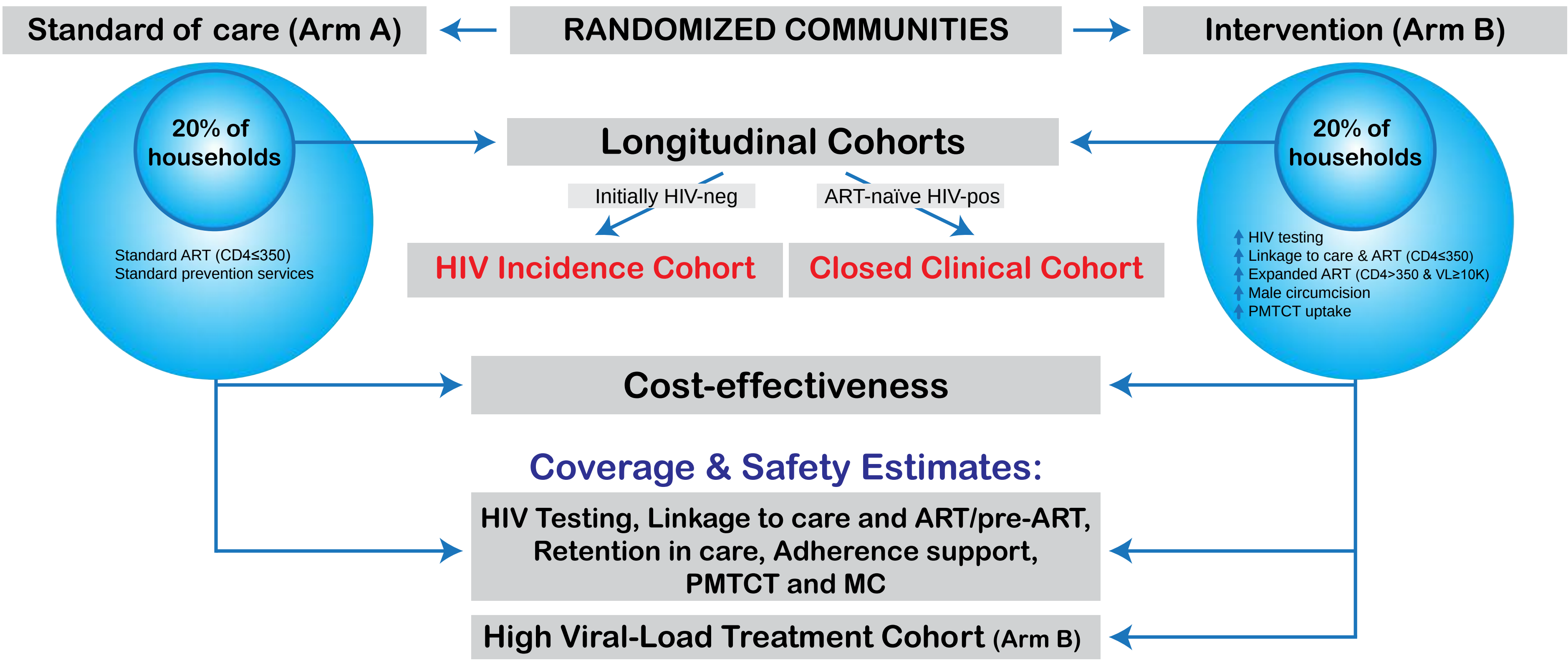
PI: Max Essex

PRIMARY OBJECTIVES:

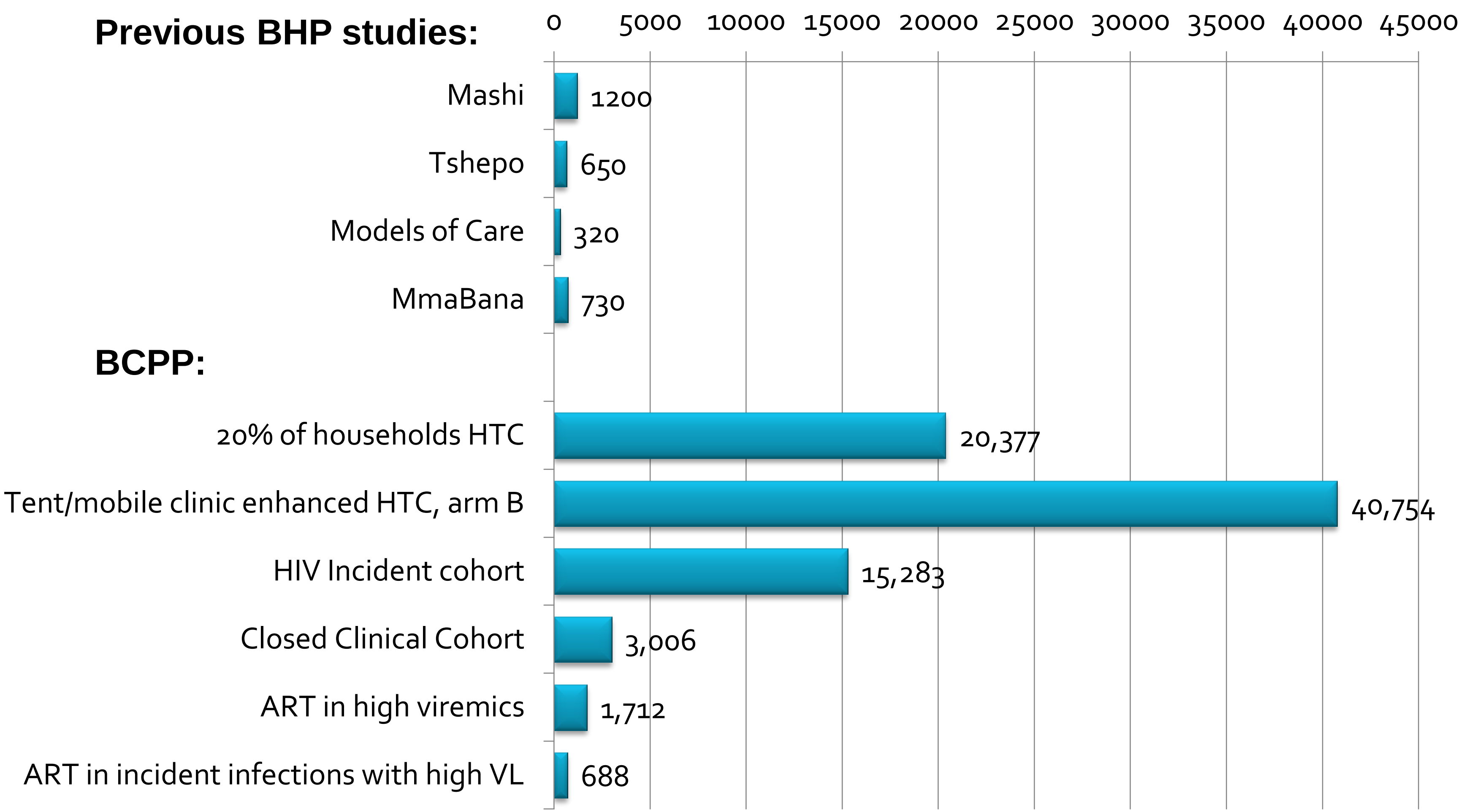
- To reduce cumulative HIV incidence in adults (16–64 years old) by:
  - Enhanced HIV testing and counseling (HTC);
  - Active linkage to HIV care and treatment;
  - Expanded MC services;
  - cART for adults with CD4<350/µL or WHO stage III/IV, or with HIV-1 RNA load ≥10,000 copies/ml (with viral linkage);
  - PMTCT:
    - early initiation of ART during pregnancy in HIV-positive women
    - retesting of HIV-negative women late in pregnancy
- To estimate the cost per infection averted

Botswana Combination Prevention Project

PI: Max Essex



BHP studies and BCPP



Conclusions

- **HIV-1 viral linkage** and **HIV-1 RNA load** are important components of the **TasP** strategy.
- The major role of **viral linkage**:
  - to distinguish linked and unlinked cases
  - to determine the extent of mixing across communities.
- Monitoring of **HIV-1 RNA load** can:
  - re-focus the TasP strategy on the most likely transmitters
  - reduce the cost of the TasP approach over time.

TasP reviews

PLoS MEDICINE

Review

HIV Treatment as Prevention: Issues in Economic Evaluation

Till Bärnighausen[1,2*], Joshua A. Salomon[1], Nalinee Sangrujee[3]

Review

HIV Treatment as Prevention: Considerations in the Design, Conduct, and Analysis of Cluster Randomized Controlled Trials of Combination HIV Prevention

Marie-Claude Boily[1*], Benoît Mâsse[2], Ramzi Alsallaq[3], Nancy S. Padian[4,5], Jeffrey W. Eaton[1], Juan F. Vesga[1], Timothy B. Hallett[1]

Review

HIV Treatment as Prevention: Debate and Commentary—Will Early Infection Compromise Treatment-as-Prevention Strategies?

Myron S. Cohen[1,2,3¶], Christopher Dye[4¶], Christophe Fraser[5¶*], William C. Miller[2,3¶], Kimberly A. Powers[2,3¶*], Brian G. Williams[6¶*]

TasP reviews

PLoS MEDICINE

Review

HIV Treatment as Prevention: Optimising the Impact of Expanded HIV Treatment Programmes

Wim Delva[1,2*], Jeffrey W. Eaton[3], Fei Meng[2,4], Christophe Fraser[3], Richard G. White[5], Peter Vickerman[6], Marie-Claude Boily[3], Timothy B. Hallett[3]

Review

HIV Treatment as Prevention: Principles of Good HIV Epidemiology Modelling for Public Health Decision-Making in All Modes of Prevention and Evaluation

Wim Delva[1], David P. Wilson[2], Laith Abu-Raddad[3,4,5], Marelize Gorgens[6], David Wilson[6], Timothy B. Hallett[7], Alex Welte[1*]

Review

HIV Treatment as Prevention: Modelling the Cost of Antiretroviral Treatment—State of the Art and Future Directions

Gesine Meyer-Rath[1,2*], Mead Over[3]

TasP reviews

PLoS MEDICINE

Review

HIV Treatment as Prevention: The Utility and Limitations of Ecological Observation

M. Kumi Smith[1], Kimberly A. Powers[1,2], Kathryn E. Muessig[2], William C. Miller[1,2], Myron S. Cohen[1,2,3]*

Review

HIV Treatment as Prevention: Models, Data, and Questions—Towards Evidence-Based Decision-Making

The HIV Modelling Consortium Treatment as Prevention Editorial Writing Group*

Review

HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention

David P. Wilson*

Mochudi Prevention Project: Study Team

Mochudi Prevention Project:
Home-Based Counselors & Recruiters

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Mompati Mmalane
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HSPH team, Boston

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Shahin Lockman
Ric Marlink
Roger Shapiro
Molly Pretorius Holme
Mary Fran McLane
Lauren Margolin
Lauren Buck
Rebeca Plank
Rui Wang
Victor DeGruttola & his group
Max Essex

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

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R37 AI24643
D43 TW000004

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Fogarty International Clinical Research Scholars & Fellows Support Center @ Vanderbilt