

Community Viral Load

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Outline

- Definition of CVL
- Relationship of VL with HIV transmission
- Definition of “Community”
- Measures
- Sources of data
- Applications
- Critiques and limitations
- Future directions for CVL

DEFINITION OF COMMUNITY VIRAL LOAD (CVL)

Definition of CVL

- Aggregate biomarker of a community's viral burden over a specific time period
 1. Indicator of a community's level of infectiousness or viral burden and transmission probability
 2. Measure of the effectiveness of combination HIV prevention care and treatment interventions
 3. Proximal marker for HIV incidence and potential epidemic propagation

RELATIONSHIP OF VL WITH HIV TRANSMISSION

Viral Load Directly Predicts HIV Transmission

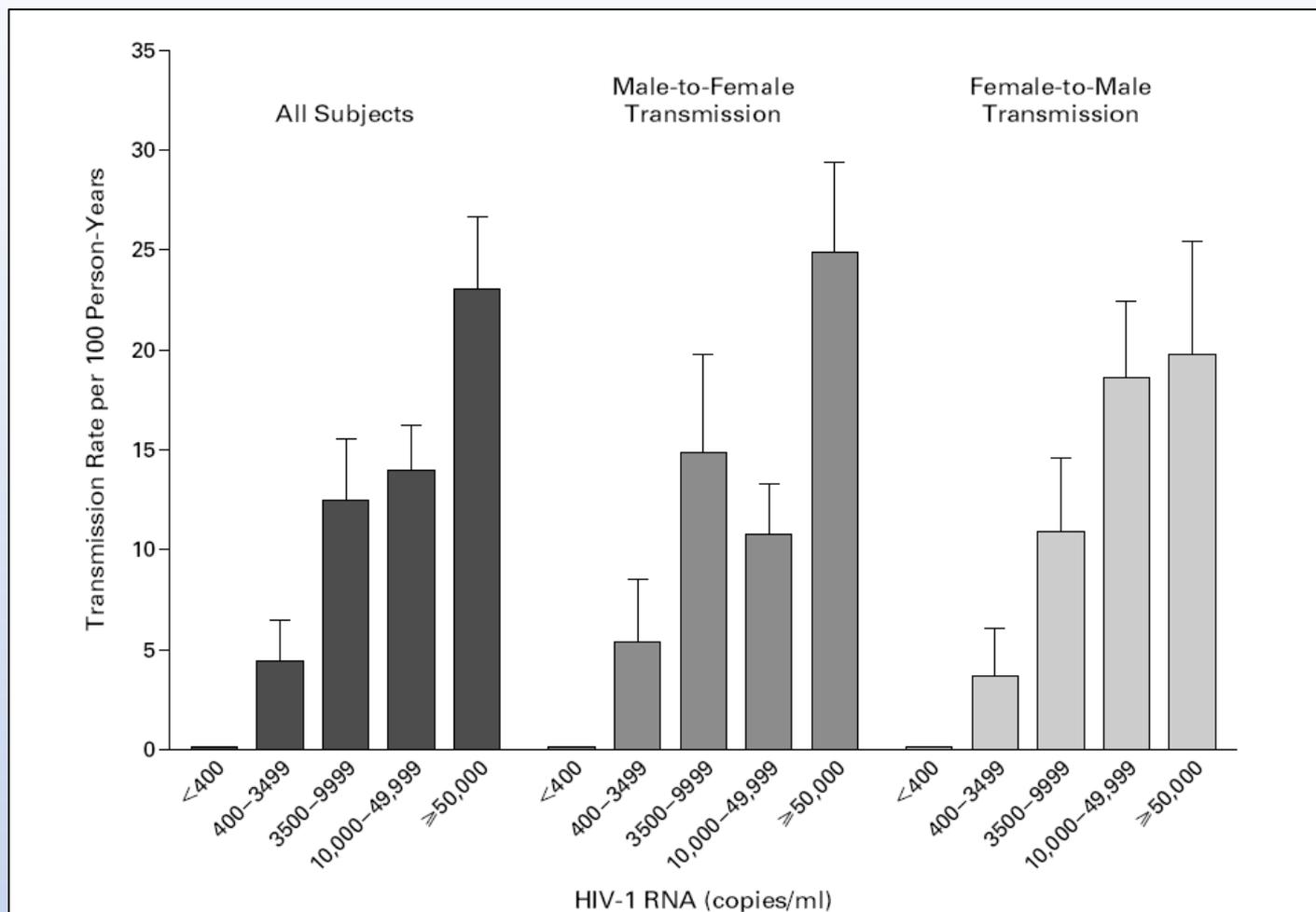
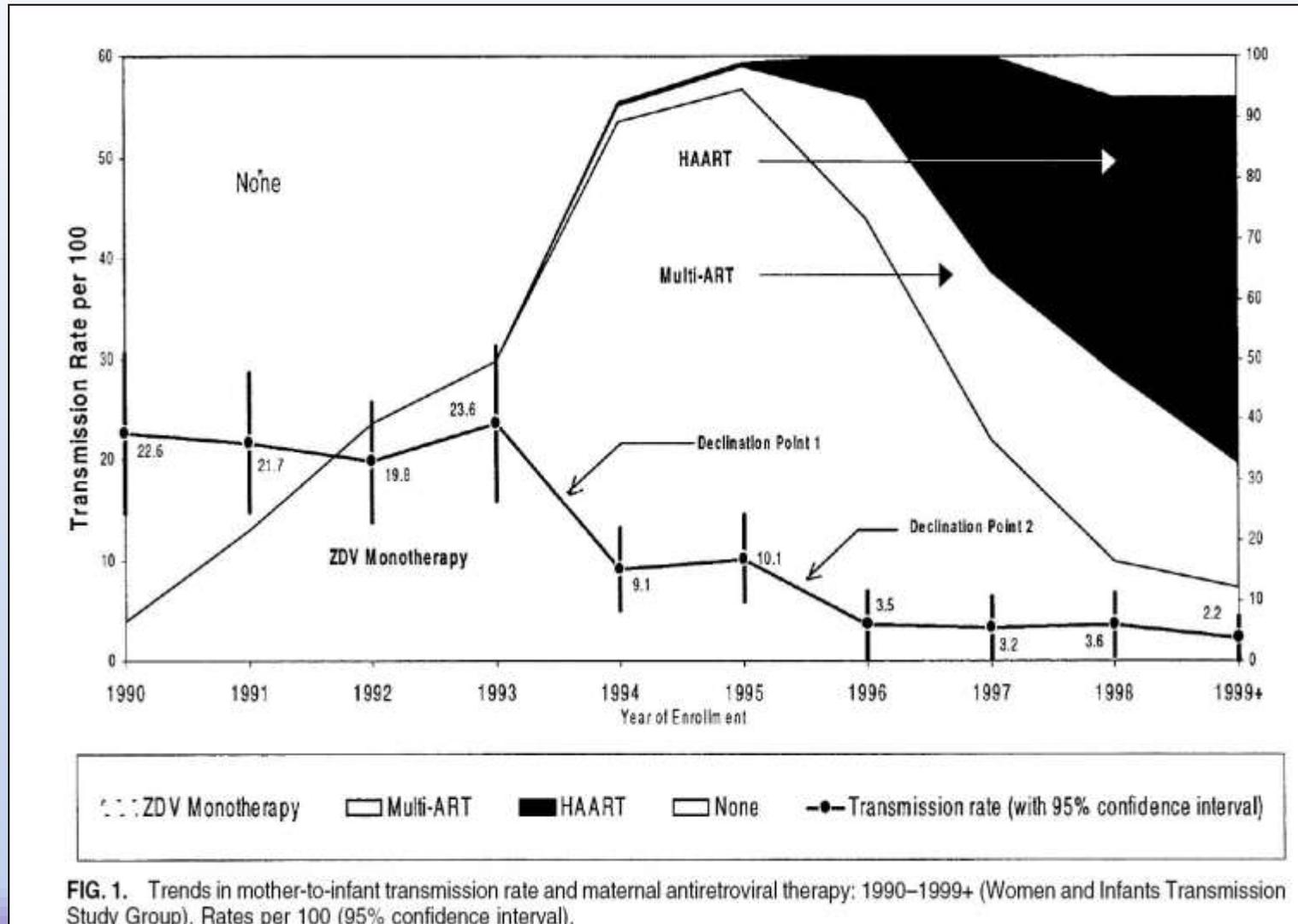


Figure 1. Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1-Positive Partner.

At base line, among the 415 couples, 228 male partners and 187 female partners were HIV-1-positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

Universal Testing and ART-Mediated Virologic Suppression Near Eliminates Perinatal Tx



ART-mediated Virologic Suppression Near Eliminates Sexual Tx

ART and HIV-1 transmission

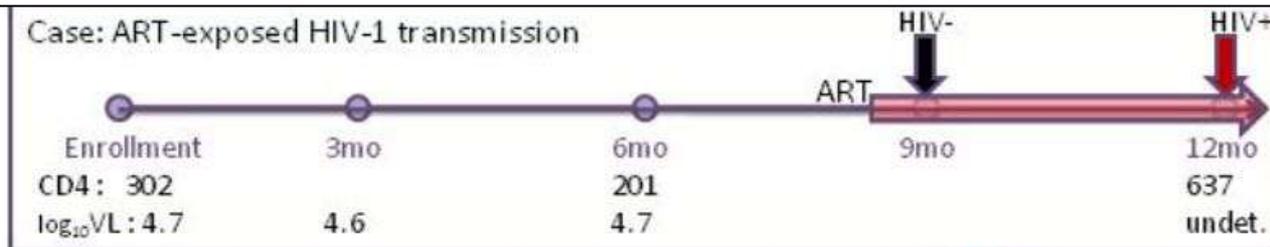
The **NEW ENGLAND**
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AUGUST 11, 2011

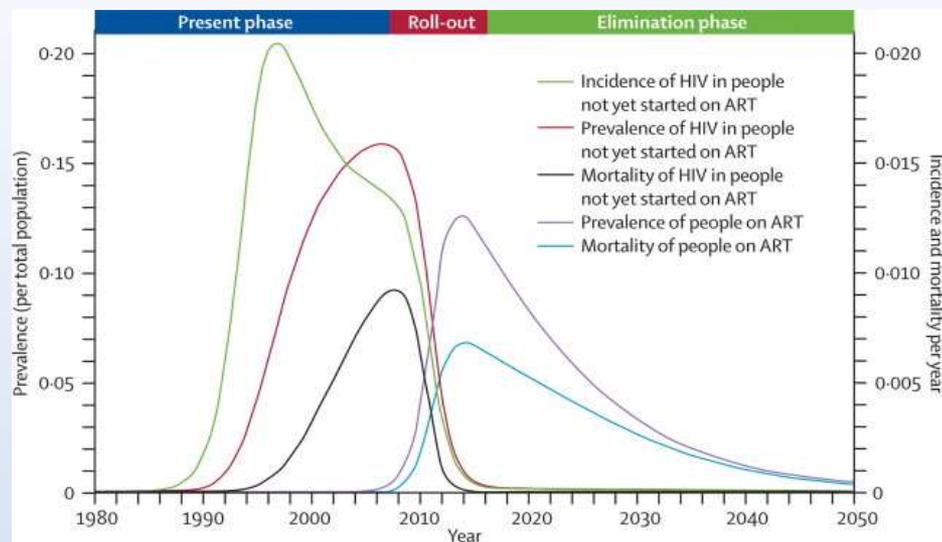
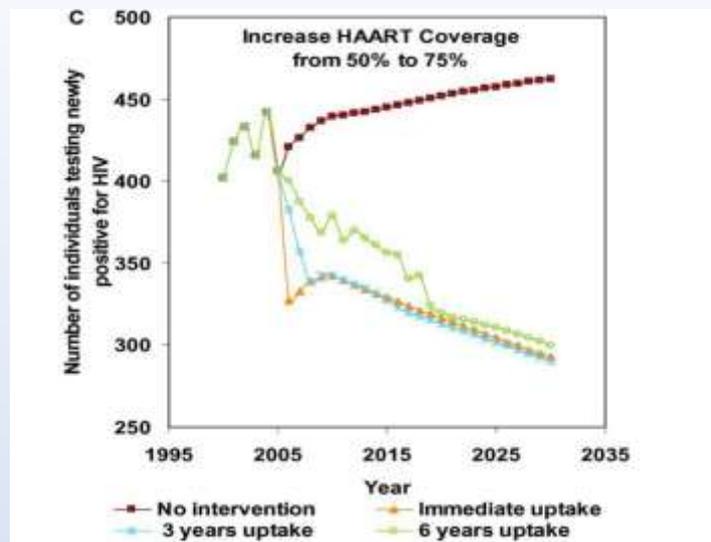
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Prevention of HIV-1 Infection with Early Antiretroviral Therapy

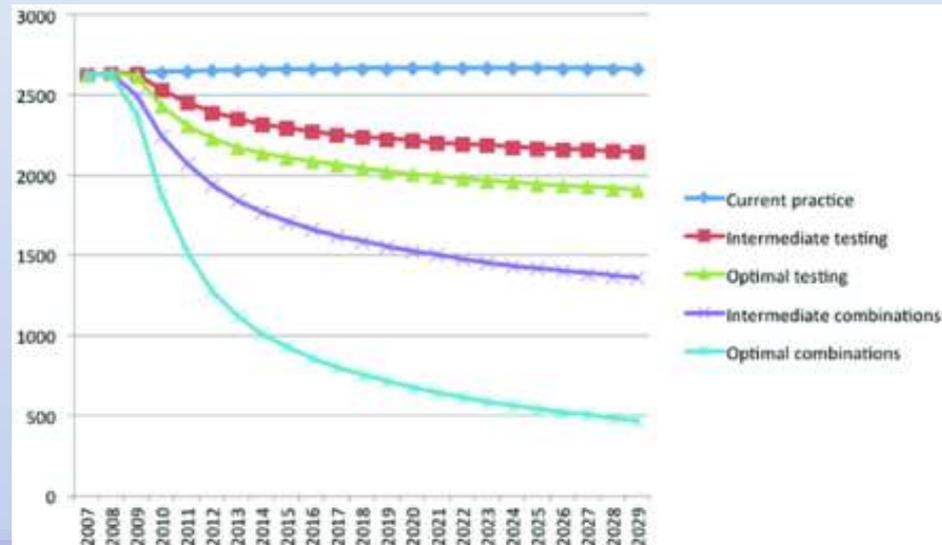


UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS IN PREVENTION

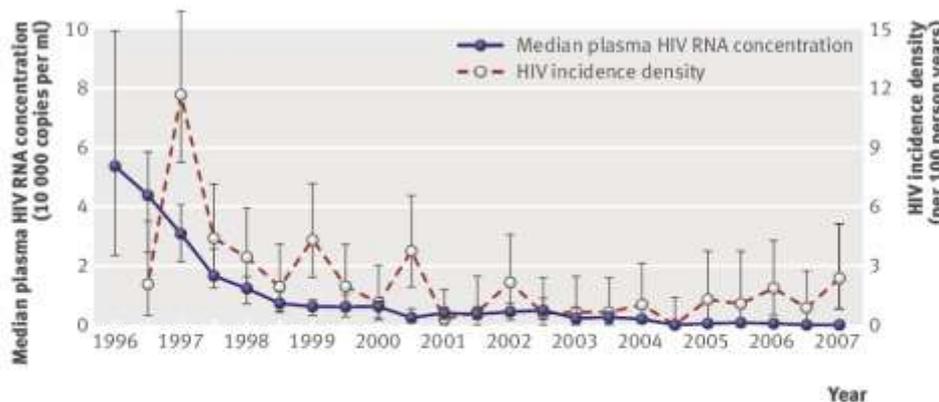
Modeling Suggests ART-mediated Virologic Suppression Reduces HIV Transmission



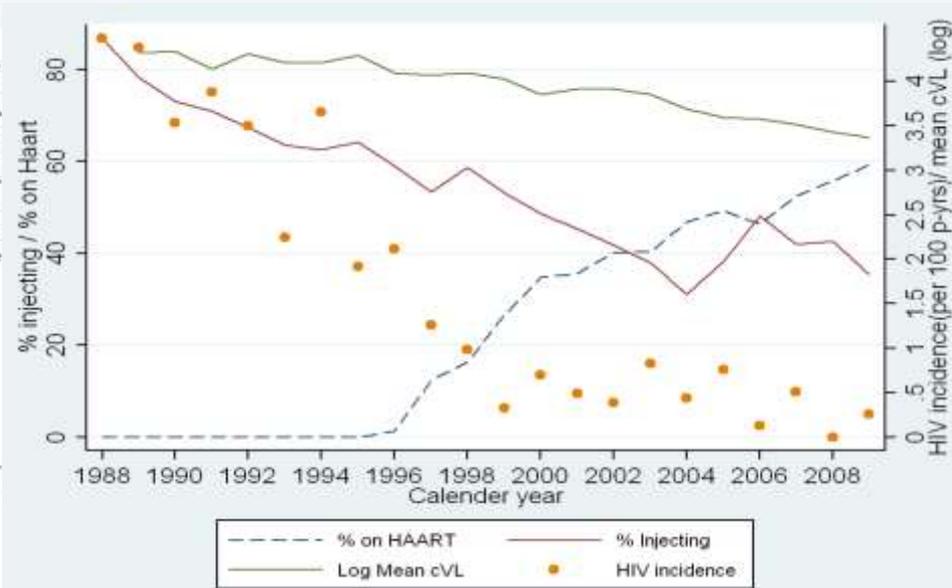
Infections Averted	Tx<500			Tx All			Test & Tx All				
	2014	2019	2029	2014	2019	2029	2014	2019	2029		
	1,554	3,102	4,940	2,169	4,550	8,221	2,810	6,040	12,189		
Percent Reduction in New Infections	Tx<500			Tx All			Test & Tx All				
	2014	42%	2019	42%	2029	33%	2014	59%	2019	61%	2029



Two Cohort Studies Demonstrate Reduced Cohort VL predicts decreased HIV Incidence

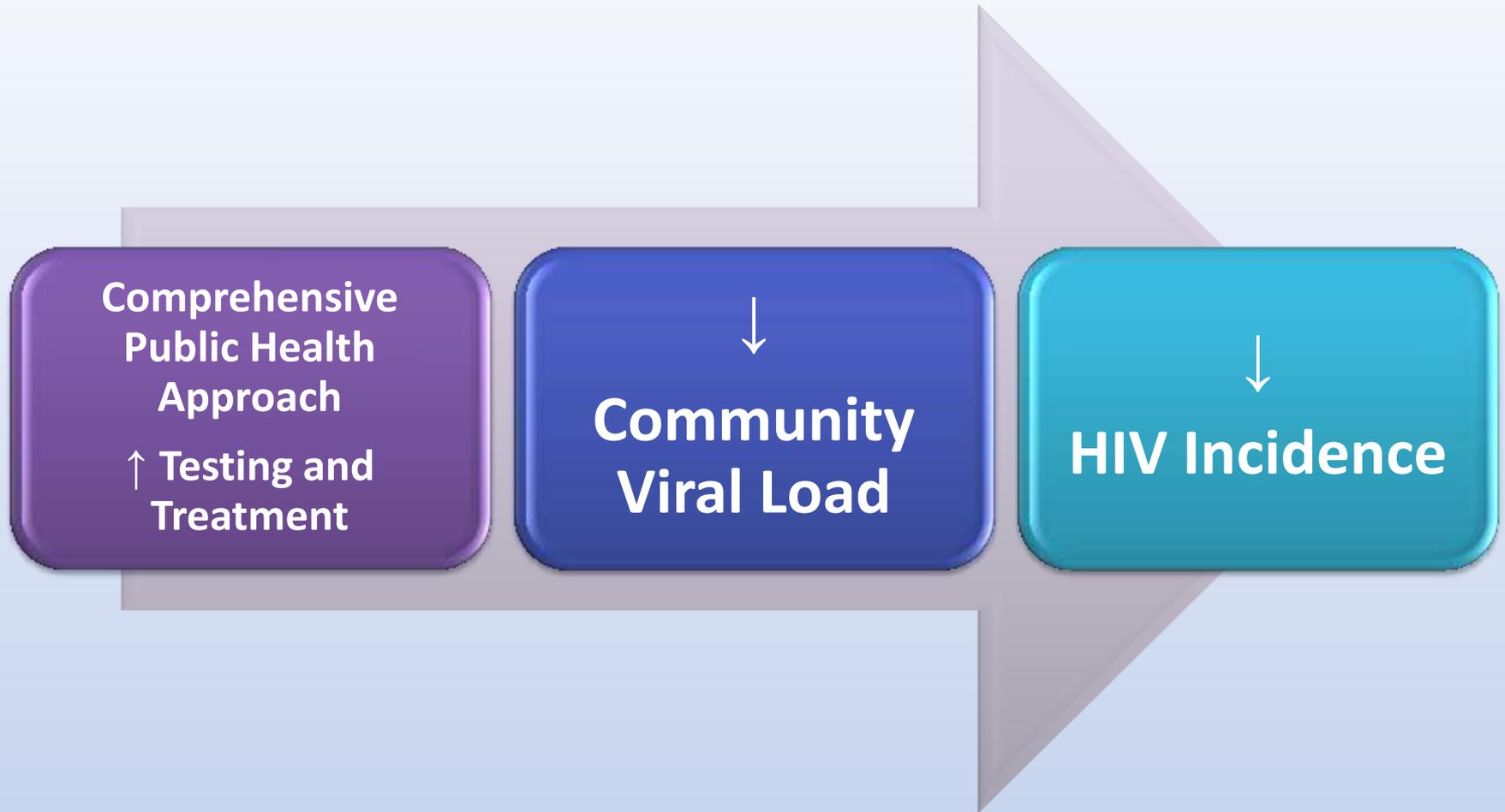


Estimated community plasma HIV-1 RNA concentrations and HIV incidence density, with 95% confidence intervals, among two parallel cohorts of injecting drug users. HIV incidence first estimated in second half of 1996 as enrolment started in May 1996 and repeat HIV tests to assess incidence were available only after six months of follow-up



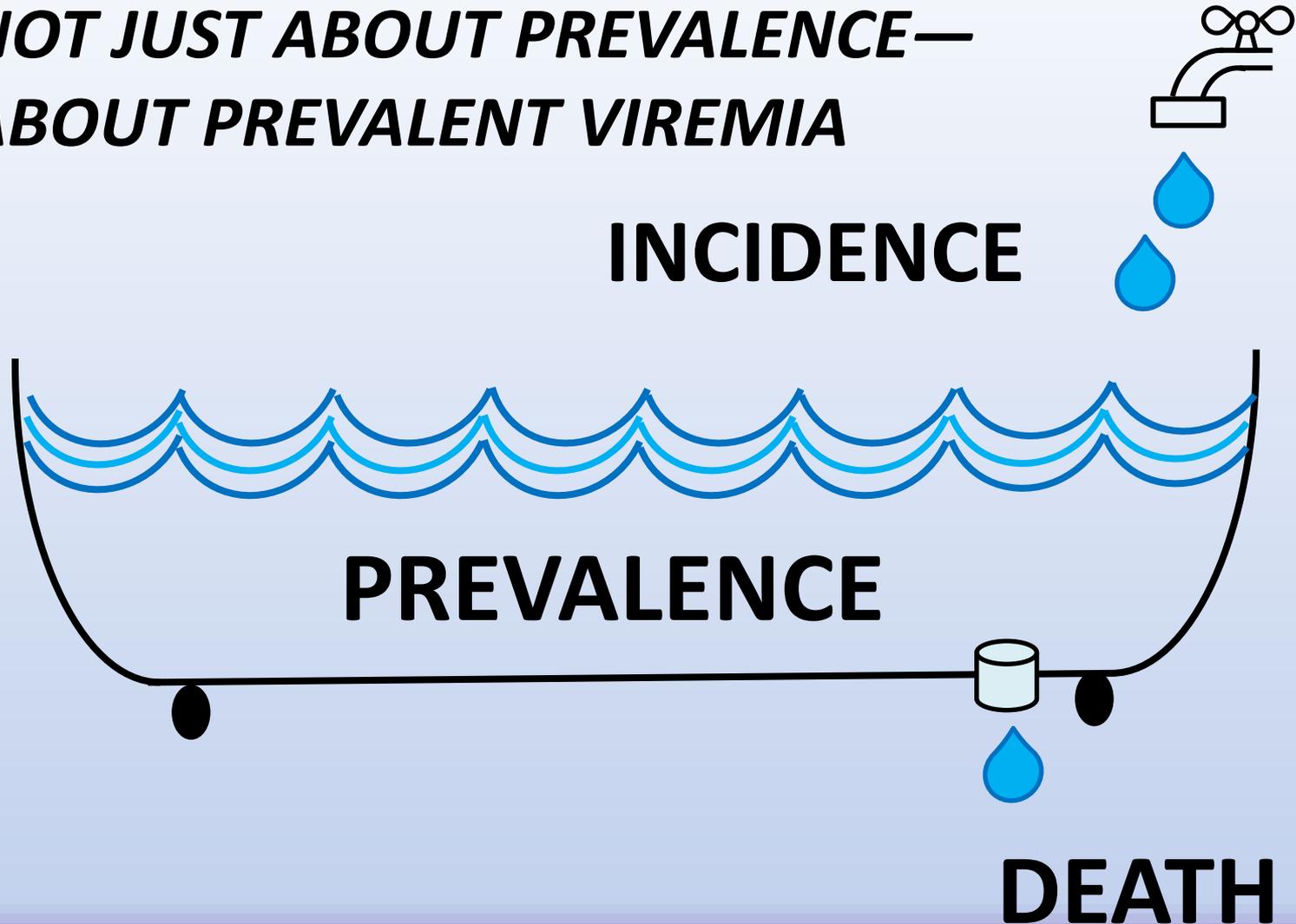
Taken together, current observational, modeling, and randomized control data demonstrates that ART-mediated virologic suppression reduces transmission at an individual level and strongly suggests community or population level effect.

The Hypothesis



Prevalence = Incidence x Duration

***NOT JUST ABOUT PREVALENCE—
ABOUT PREVALENT VIREMIA***



Definition of “Community”

- Although people who inject drugs (PWID), men who have sex with men (MSM), or specific ethnicities may not necessarily constitute a “community” in the sense of complete social interconnectedness or shared networks, we use the term “community” broadly to refer to populations defined by:
 - Demographics
 - Geography
 - Country, Province/State, City, Neighborhood, or Census tract
 - Behavioral commonality with elevated probability of connections to other members of the population, including those through needle-sharing or sexual partnerships

Calculating CVL

$$CVL = \left(\frac{\sum_{i=1}^N (VL)}{N} \right)$$

- Sum total of Unique VLs of the PLWH
- N= total number of PLWH

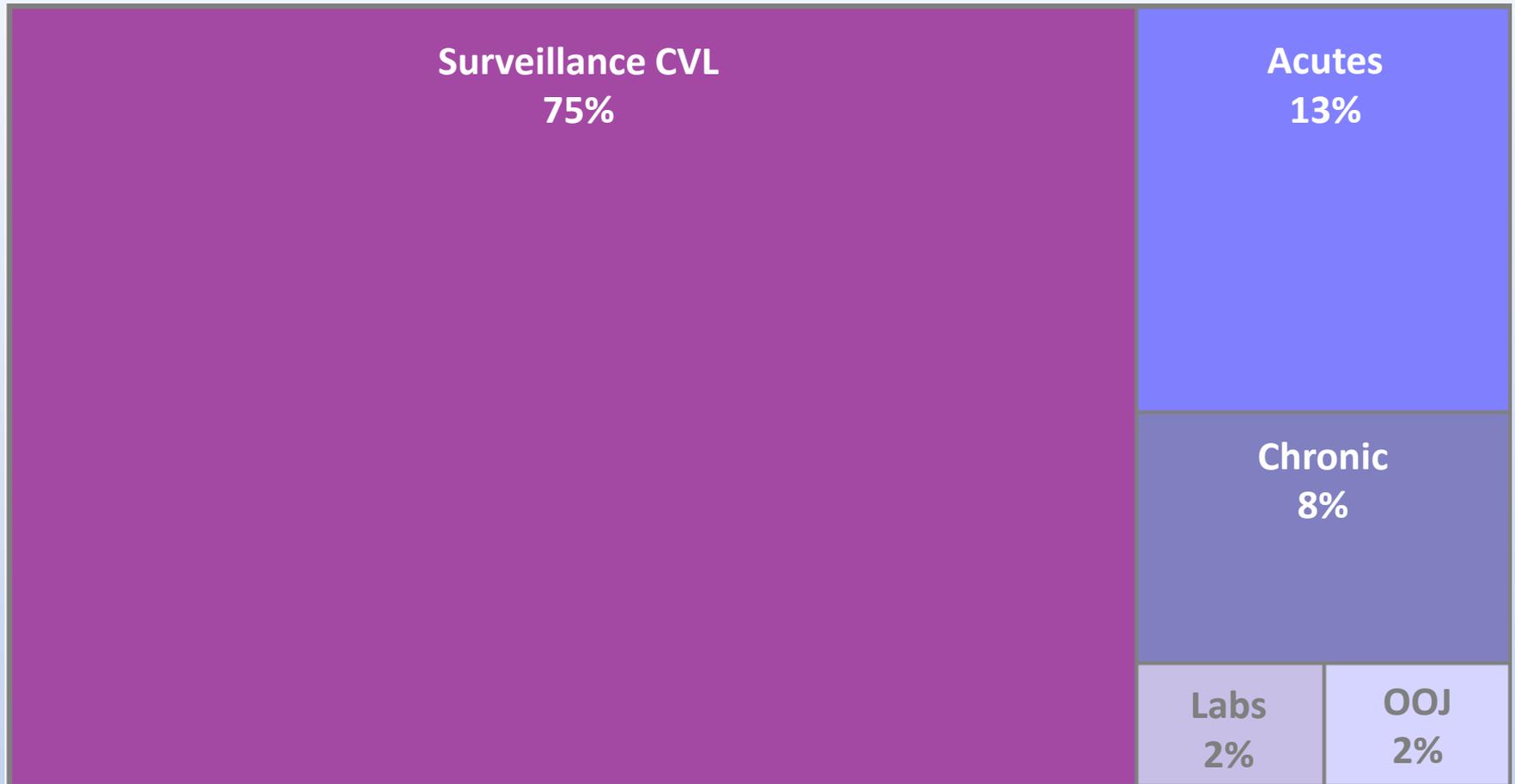
CVL Measures

CVL Measure	Use	Caveats/Limitations
Mean (Most Recent)	Useful for comparisons between sub-populations (e.g. disparities)	Influenced by outliers
Mean (of the Mean)	Useful for comparisons between sub-populations (e.g. disparities)	Multiple measurements (e.g. those started on ART, trended towards suppression in yr)
Median	ART uptake and treatment effectiveness	If >50% of VLs are undetectable, then the median is undetectable; limits analyses
Maximum (Peak)	Most conservative estimate of viral burden	Could overestimate true average burden
Minimum	Least conservative or most optimistic estimate of viral burden	Could underestimate true average burden
Total (Sum of Most Recent)	The prevalent viremia: takes into account both number of PLWHA and magnitude of the most recent VL	Proportion missing VLs can have greater influence
Time-Weighted Average	Alternate approach to handling multiple measures in year	
Population Virologic Suppression	Eval universal tx policies @ the pop level	Includes all comers, including those not on tx
Maximal Virologic Suppression	Eval HIV quality of care among those on ART for a given time	Includes only those on tx for particular time period, more helpful for care
Log transformation of any of the above measures	Reduces the influence of outliers	

Sources of Data

- Clinic
 - Individual clinic
 - Clinic/Medical system/Regional
 - Federal (VA) or National (e.g. Kaiser)
- Cohort
 - IDU (Vancouver, ALIVE, NA-ACCORD)
- Surveillance
 - Jurisdictional/State
 - Province/Country Level data

Community Viral Load



Applications

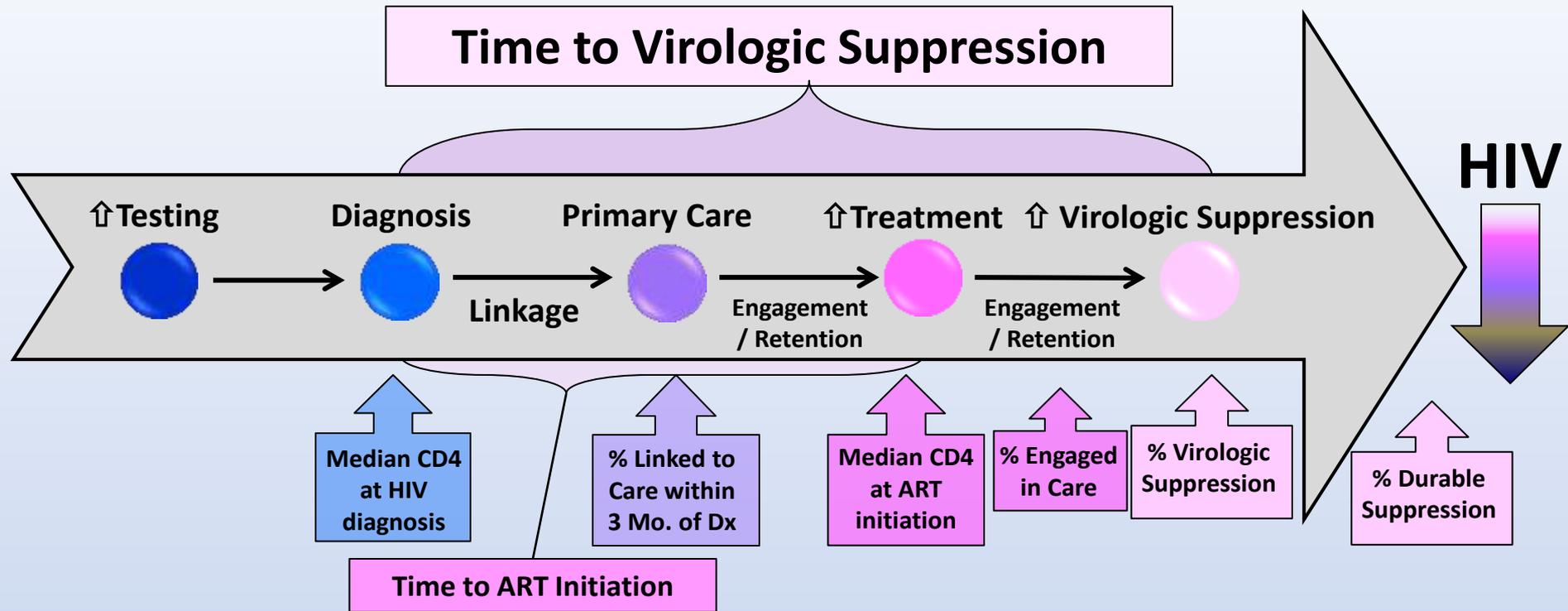
1. Indicator of a community's level of infectiousness or viral burden and transmission probability
2. Measure of the effectiveness of combination HIV prevention care and treatment interventions
3. Proximal marker for HIV incidence and potential epidemic propagation

How has CVL been used?

- Calculate cross-sectional CVL and examine geographic distribution and other disparities
 - San Francisco (*Das CROI 2009, CROI 2010, PLoS 2010*)
 - Washington, DC (*Castells, CROI 2011*)
 - New York (*Laraque, CROI 2011*)
- Calculate annual measures of CVL and relate to new HIV Infections (Program and Research)
 - Cohort (Vancouver, Baltimore)
 - Surveillance/Ecologic

SAN FRANCISCO HIV/AIDS STRATEGY AND USES OF CVL

Using San Francisco's Surveillance Data to Evaluate Our Continuum of Prevention, Care and Treatment



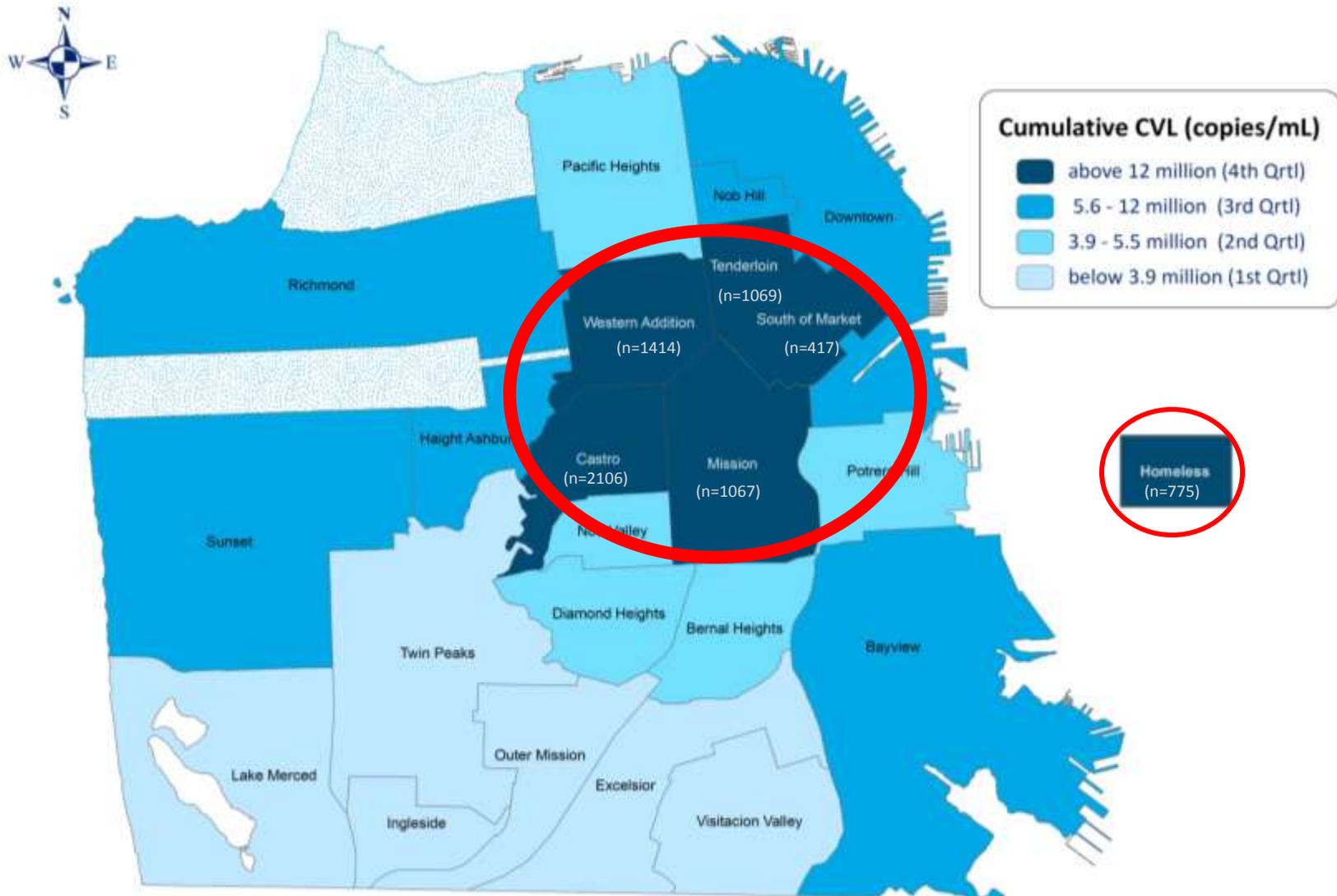
Community Viral Load: Unified
Marker of Prevention and Treatment

CVL Disparities, SF 2004-2008

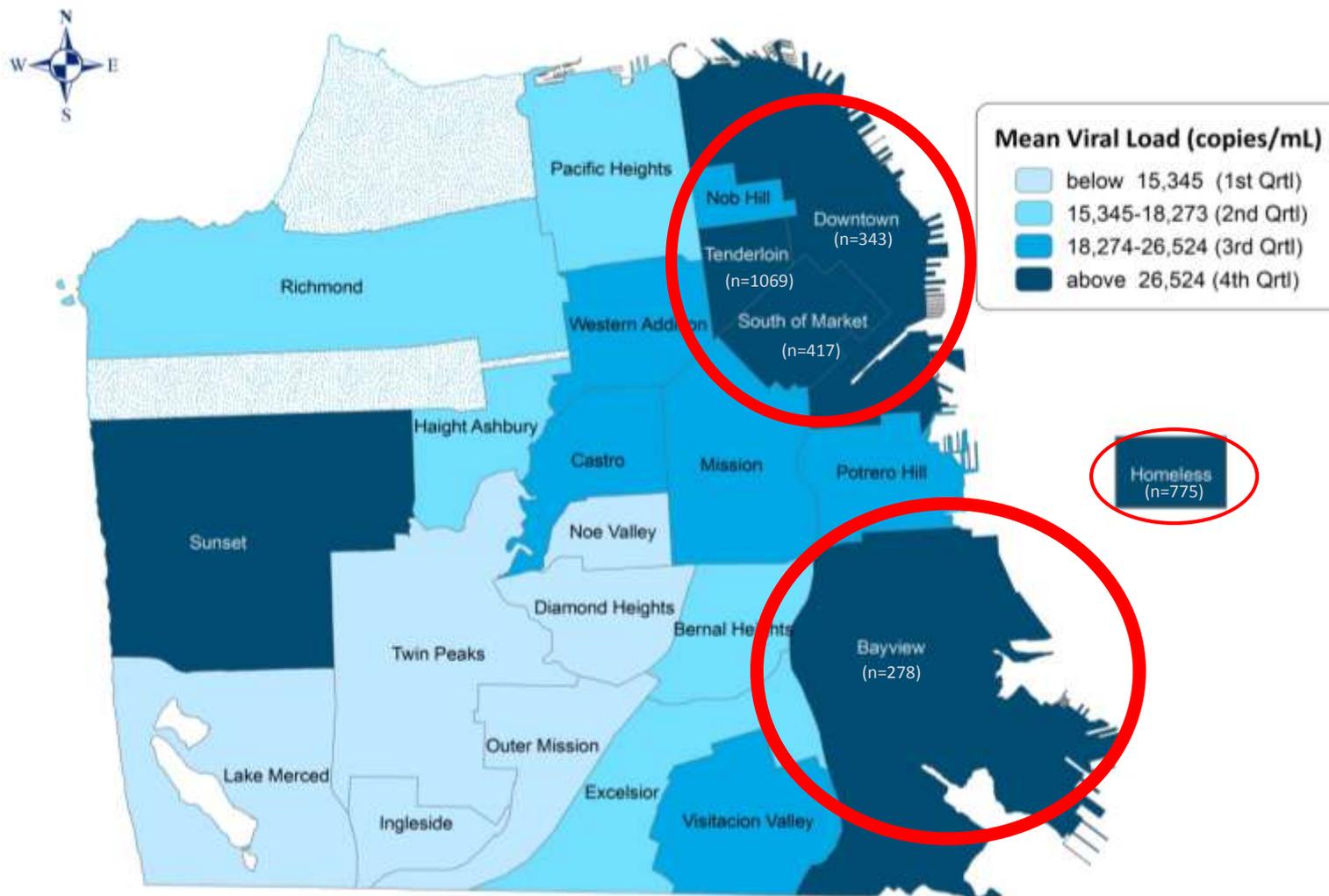
Overall	N	(%)	Mean CVL*
San Francisco	12,512	(100)	23,348
Sub-groups	N	(%)	Mean CVL*
Latino	1822	(15)	26,744
African-American	1825	(15)	26,404
Women	786	(6)	27,614
Transgender	291	(2)	64,160
IDU	1011	(8)	33,245
MSM-IDU	1791	(14)	36,261
Not on treatment	2924	(23)	40,056
Not engaged in care	4637	(37)	36,992

*(p<0.001 by Kruskal-Wallis test) in mean CVL by treatment history, race/ethnicity, age, gender, HIV transmission risk category, insurance status, and clinical status.

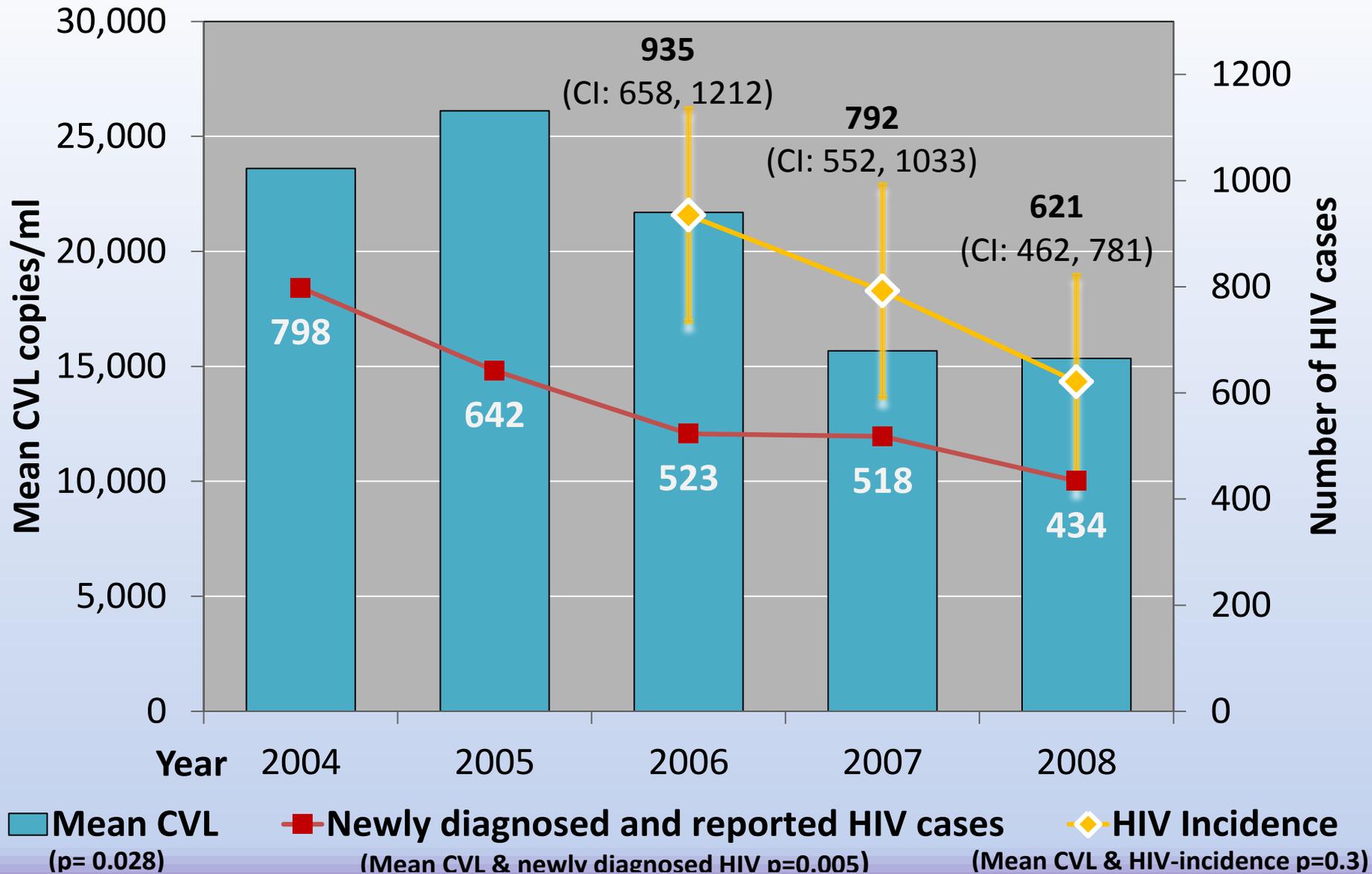
Spatial Distribution of Total CVL by Neighborhood, 2005-2008



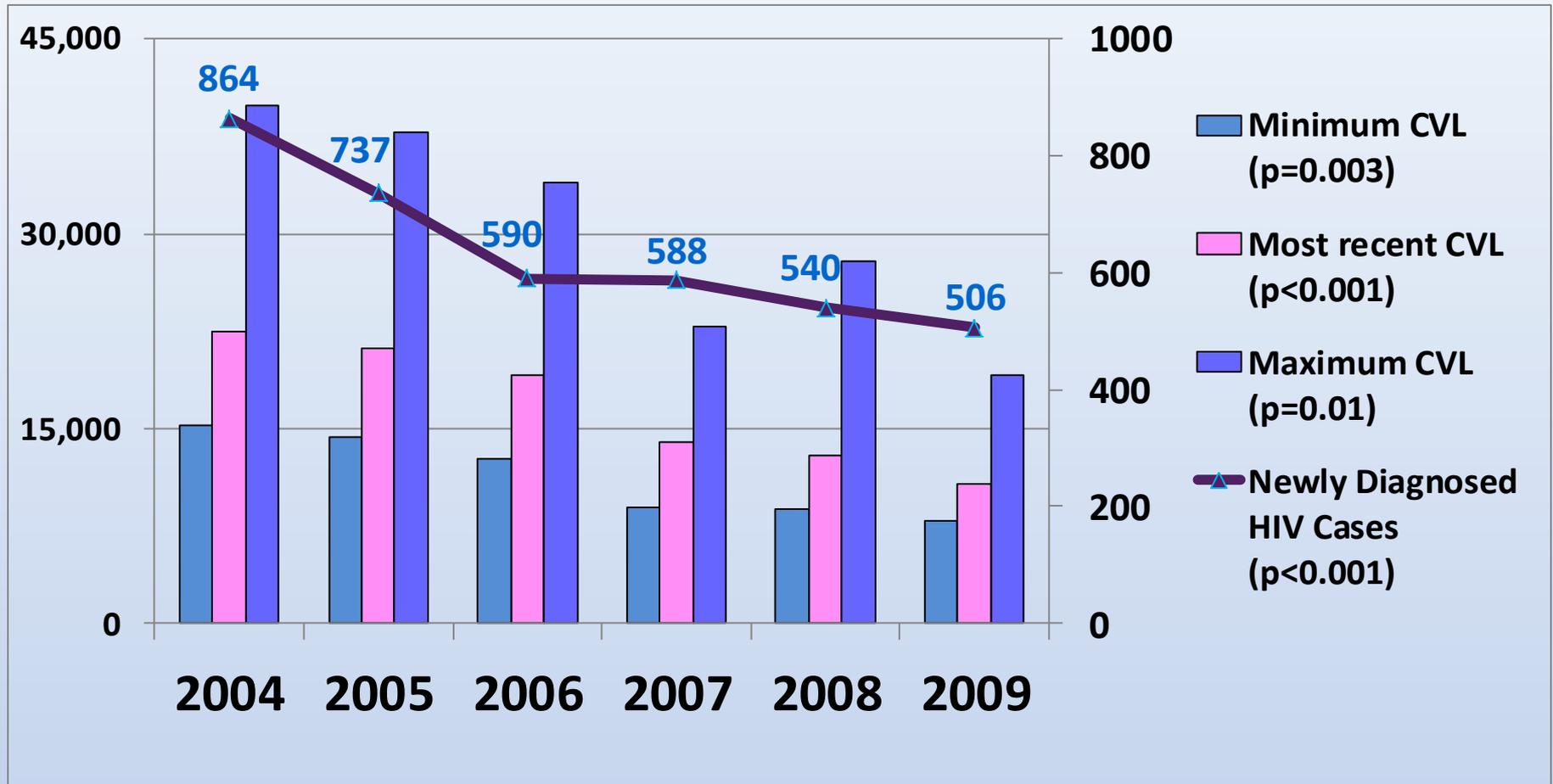
Spatial Distribution of Mean CVL by Neighborhood, 2005-2008



Mean CVL and New HIV Infections, 2004-2008

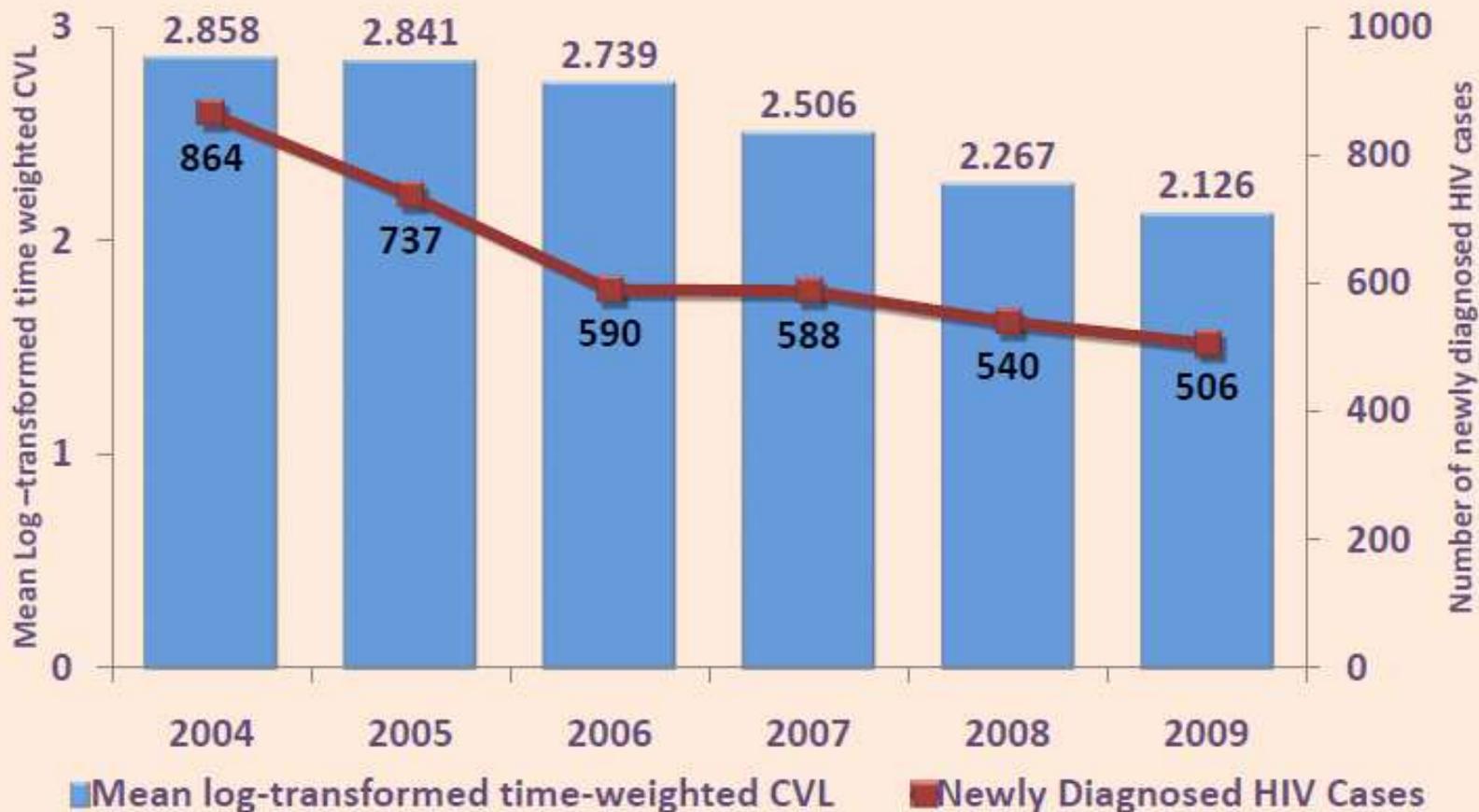


Minimum, Most Recent, Maximum CVL and Newly Diagnosed and Reported HIV cases



Refining CVL Calculation with Time-Weighted Averaging (AUC)

Mean log-transformed time-weighted CVL and Newly Diagnosed HIV cases, 2004-09



Community Viral Load Disparities

Figure 1: Spatial Distribution of Mean CVL in San Francisco, 2004-08

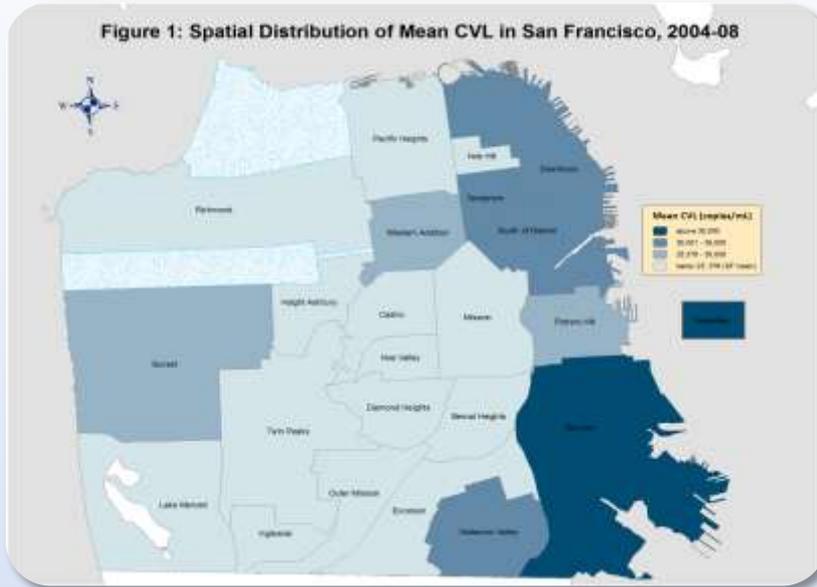
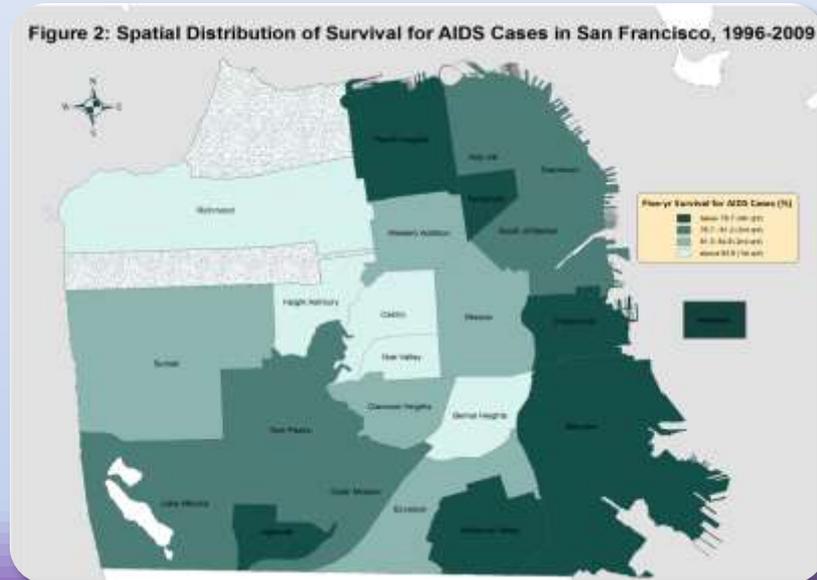


Figure 3: Spatial Distribution of Poverty in San Francisco, 2000



Figure 2: Spatial Distribution of Survival for AIDS Cases in San Francisco, 1996-2009



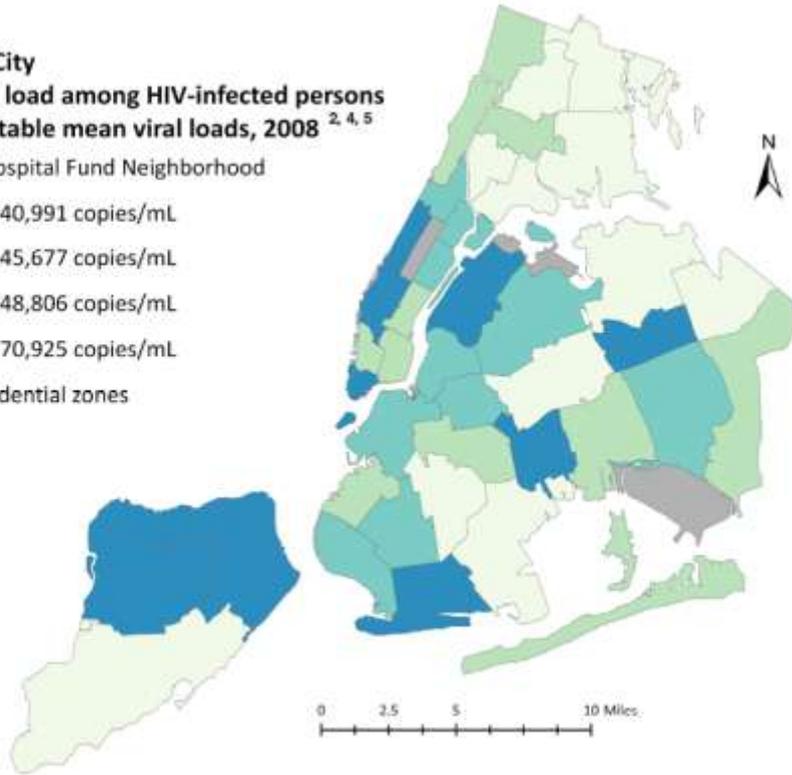
- Even in relatively richly-resourced San Francisco, disparities in CVL track with poor 5-year survival and neighborhood concentration of poverty
- CVL may be a useful marker for public health departments to target resources and address geographic disparities in HIV transmission and survival

CVL: New York & Washington D.C.

New York City
Mean viral load among HIV-infected persons
with detectable mean viral loads, 2008^{2,4,5}

by United Hospital Fund Neighborhood

- 28,335 - 40,991 copies/mL
- 40,992 - 45,677 copies/mL
- 45,678 - 48,806 copies/mL
- 48,807 - 70,925 copies/mL
- Non-residential zones

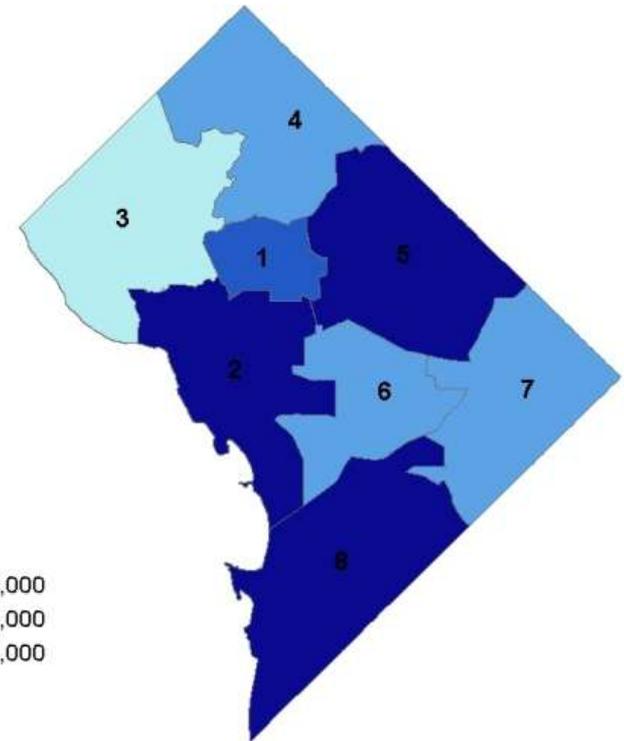


Mean Community Viral Load by Ward, 2004-2008



Mean CVL

- 0 - 25,000
- 25,000 - 48,000
- 48,000 - 53,000
- 53,000 - 71,000



Laraque, et al. CROI, 2011. Abstract #1024.

Castel, et al. CROI, 2011. Abstract #1023.

Summary of Uses of CVL

- Comparing mean CVLs of different groups highlight disparities by specific demographic, transmission risk, or geospatial characteristics
- Establishing overall and sub-group baselines and following trends can be helpful for local planning and re-allocation decisions
- Planned cluster RCTs of “test and treat” strategies can examine CVL as:
 - Marker of transmission probability
 - Effectiveness of the Strategy
 - Proximal Marker of HIV incidence

HIV Case Registry/Surveillance Concerns

- **Timeliness and completeness of reporting HIV cases**
- **Testing uptake (% undiagnosed)**
 - Chronically infected and unaware
 - Acutely infected and unaware (high VLs)
- **Missing VL data**
 - Difficult venipuncture
 - Not on ART
 - Out of care, not monitored
 - Out of jurisdiction (OOJ)
- **“Extra” VL data received but not entered into surveillance registry**
 - Cared for in jurisdiction but attributed as case of another jurisdiction
- **Unknown unknowns**
 - Moved into jurisdiction but out of care
- **Addressing Surveillance Limitations**
 - HIV Testing technology advances
 - NHBS sample of undiagnosed
 - Acute will remain an issue
 - Missing data—multiple imputation—need VL data missing at random
 - MAR may hold in the case of OOJ however, biases with difficult venipuncture, not on ART, out of care
 - Count “extra-jurisdictional cases”
 - Unknown unknowns will remain unknown

Clinical or Cohort Data Limitations

- More complete data from study or clinical databases
- Not as generalizable beyond study or clinic
- May reflect HIV quality of care more than HIV prevention or transmission potential
- Exceptions:
 - Cohort study of geographic or closed population

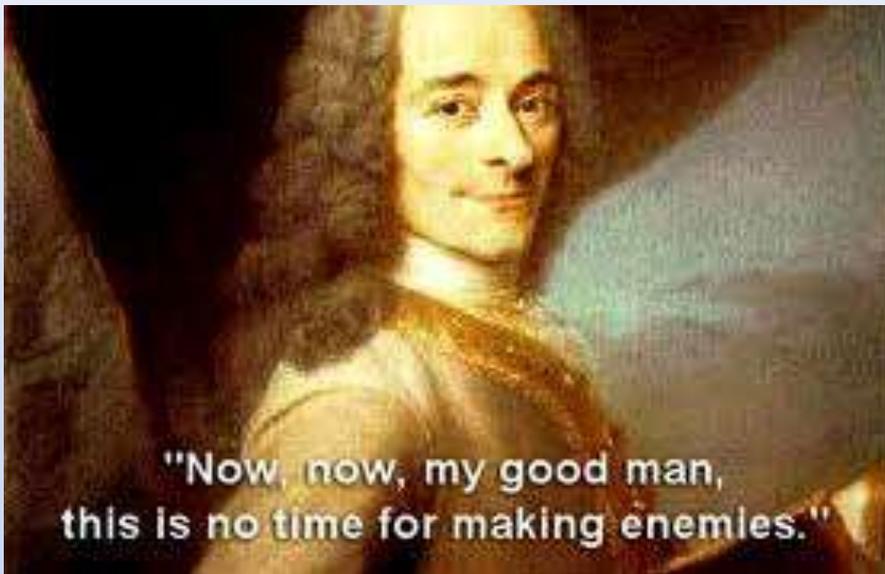
Ecologic Fallacy Limitations

- Alternative explanations for decreased HIV incidence
 - Reductions in sexual risk behavior?
 - Rectal gonorrhoea and primary/secondary syphilis trends as proxy marker (opposite direction of increased risk in many developed country epidemics)
 - Serosorting
 - HIV cases as proxy for HIV incidence
 - Reduced testing rates?
 - Testing rates increased secular trend

Let Not the Perfect Be the Enemy of the Good!

“The perfect is the enemy of the good.”

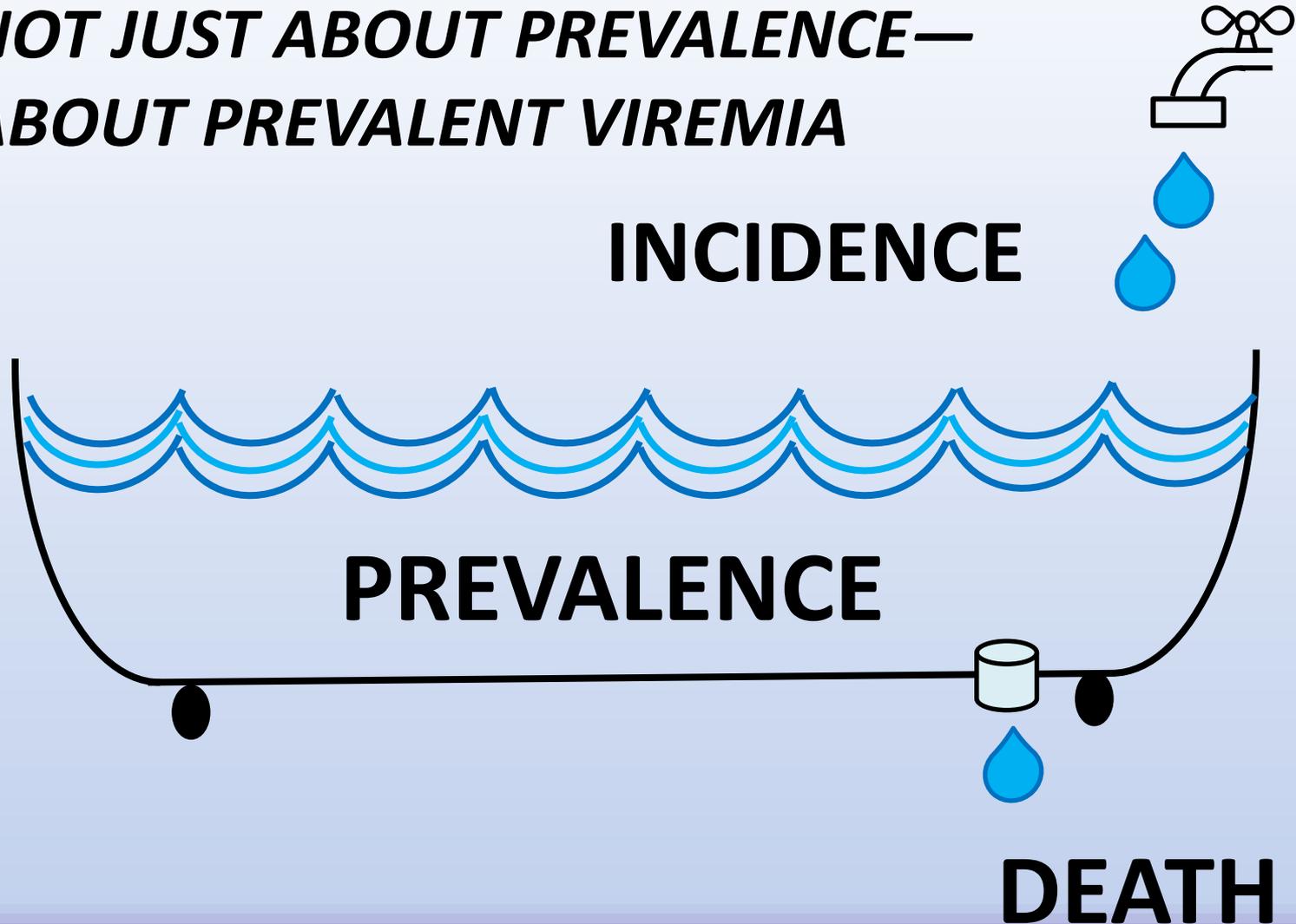
–Voltaire, 1772



FUTURE DIRECTIONS OF CVL

Prevalence = Incidence x Duration

***NOT JUST ABOUT PREVALENCE—
ABOUT PREVALENT VIREMIA***

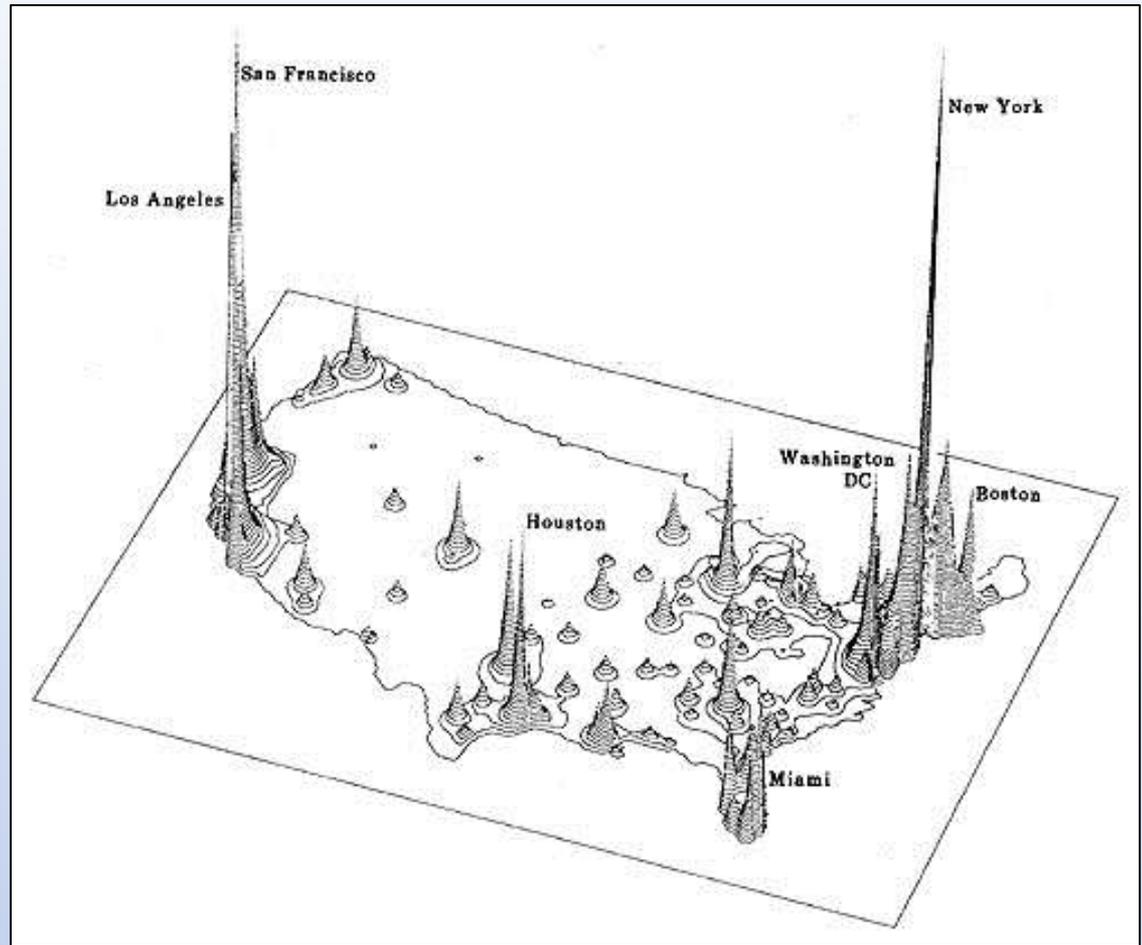


Conclusion

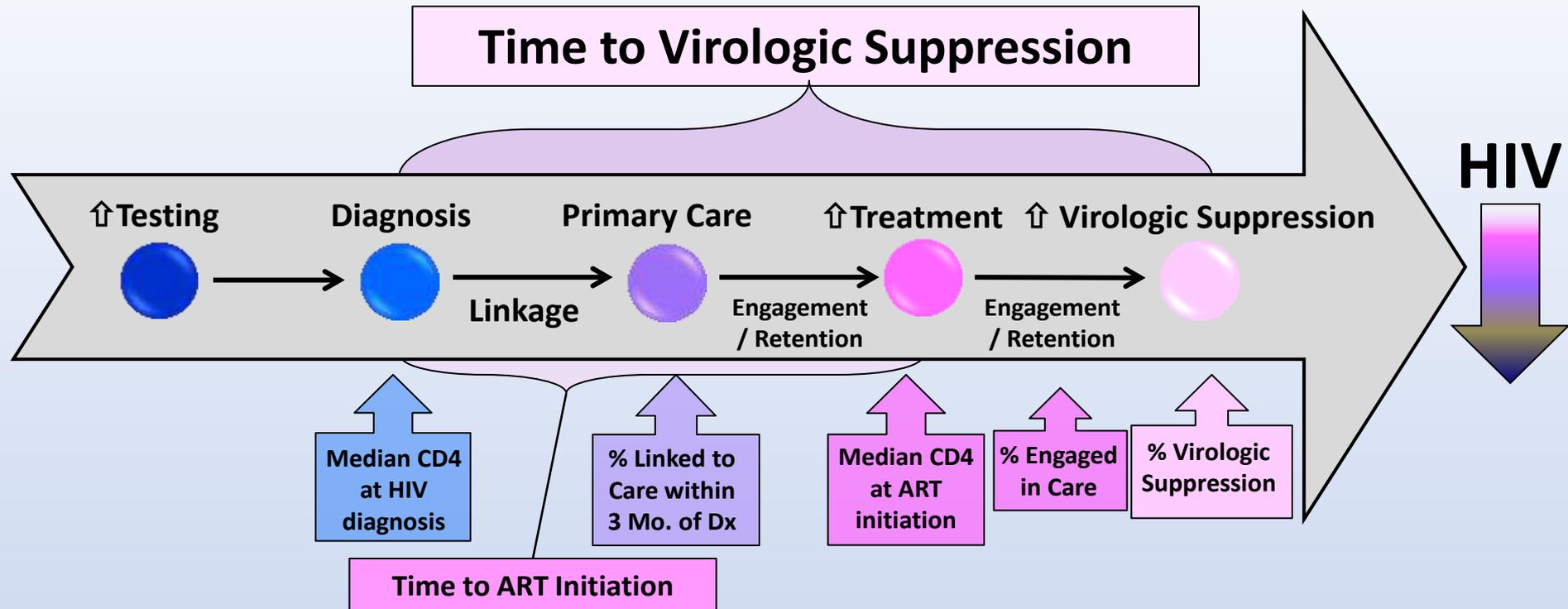
- Trends in newly diagnosed cases and HIV prevalence no longer sufficient to characterize epidemic
- Hard to measure acute HIV infections and HIV incidence
- Despite CVL limitations, measure provides additional insight particular to era of maximizing outcomes along cascade with testing, linkage, ART uptake, engagement in care efforts

Can We Get to a National or Global CVL Estimate?

- Yes, we can!
- Establish the baseline
- **Must modernize surveillance in the United States**
- We should pursue the exercise to delineate missing data, gaps in resources, technology, or other issues
- ***Follow trends in CVL → HIV Incidence***
- ***Single indicator/snapshot of Cascade efforts***
- NHAS/ACA
- International—hotspots, characterize new epidemics, TasP studies



Modeling to Augment Evaluation: CVL in each compartment including those who fall off continuum



What CVL or % Supp → $R < 1$?

Acknowledgments

People living with HIV/AIDS in San Francisco



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