The use of modeling methods and knowledge gained from alcohol behavioral research to advance HIV prevention interventions

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Alcohol Behavioral HIV Prevention Research: Mechanisms and Intervention Development
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Outline

Alcohol, co-morbid conditions, and HIV prevention

Using one condition to predict occurrence of another

- Example: Alcohol as a screening tool in the VACS

Targeting one condition to reduce risk of another

- Example: Reducing alcohol as treatment/prevention in the VACS

Targeting one condition to impact HIV prevention

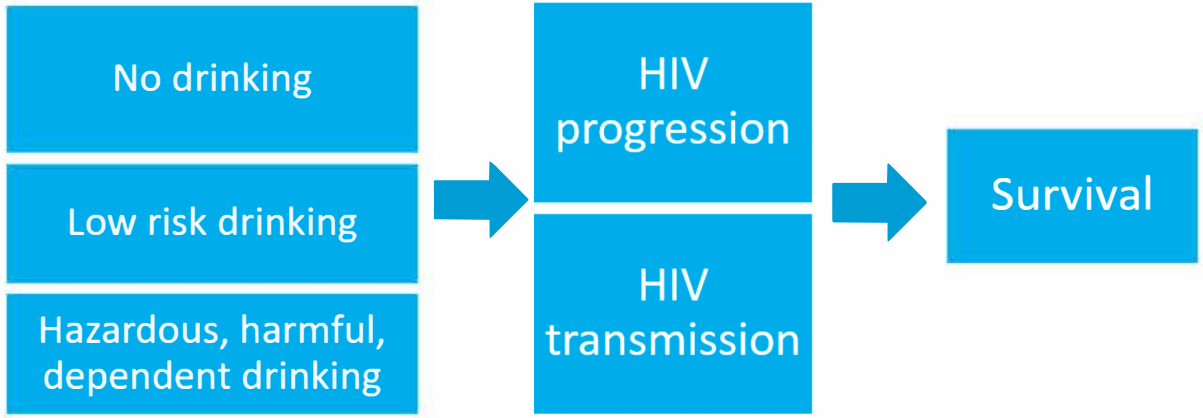
- Example: The role of mathematical modeling

Alcohol and HIV interventions

Alcohol consumption common in the general US population

Unhealthy alcohol consumption leads to worse HIV progression and more rapid HIV transmission

Interventions to reduce unhealthy alcohol consumption could prevent a large proportion of new infections and AIDS-related deaths

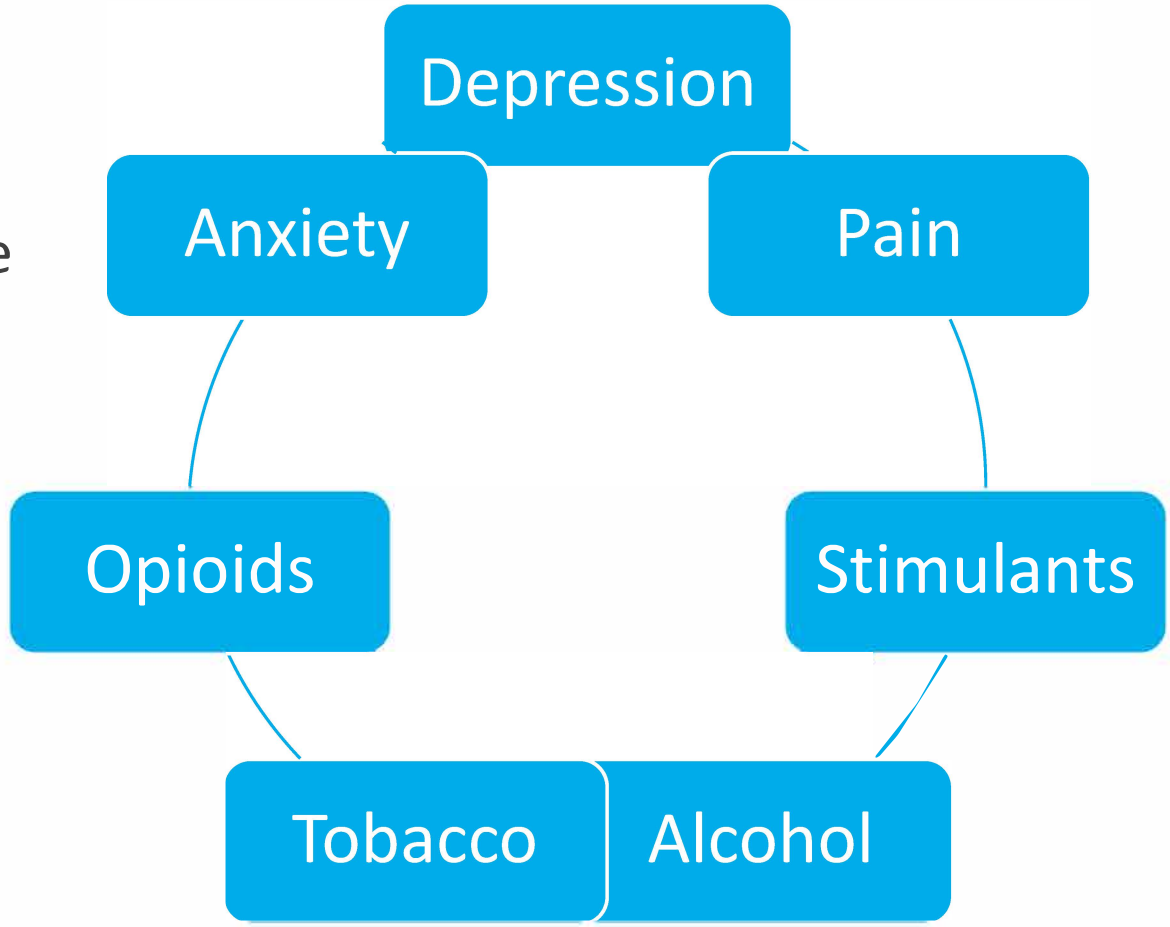


Co-morbid conditions

Conditions that often occur together

Sources of preventable morbidity and mortality

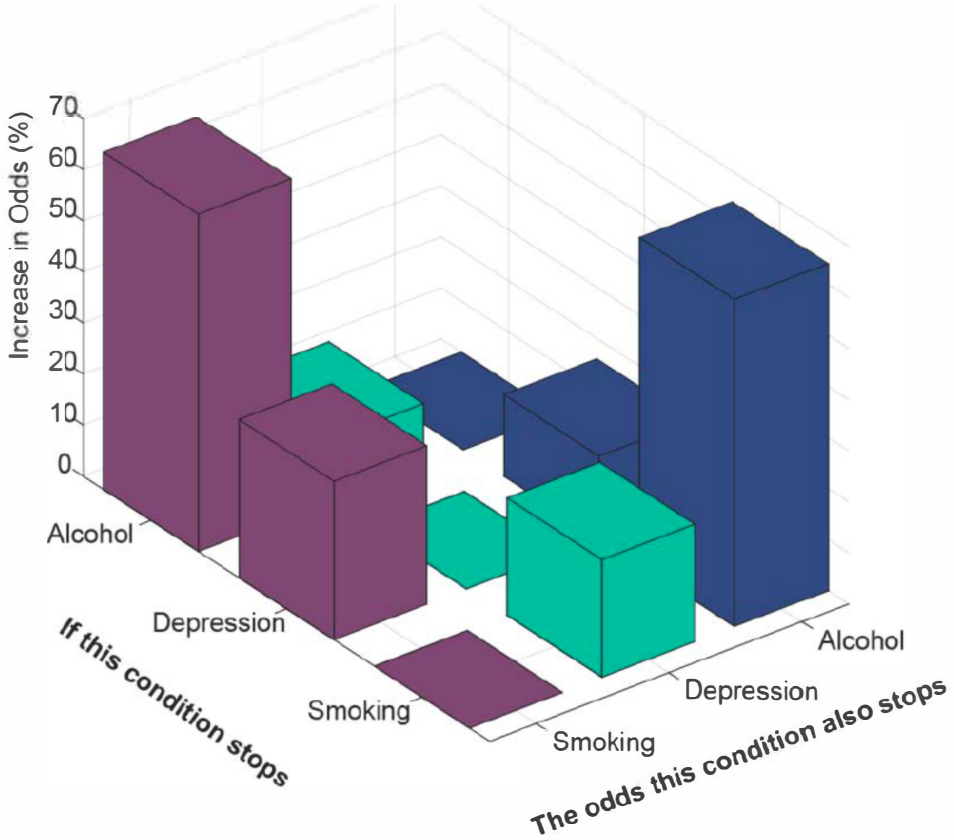
May increase HIV transmission or progression



Alcohol, co-morbid conditions, and HIV prevention

Alcohol, depression, smoking often remit and recur together

Discontinuation of any of the three characteristics associated with discontinuation of any of the other two characteristics



Braithwaite et al. *AIDS Behav.* 2016

Alcohol and HIV interventions

Ideally, randomized clinical trials would evaluate alcohol-related treatment and screening strategies to reduce HIV transmission, morbidity and mortality

When clinical trials are not feasible, observational data and computer simulation can be used to identify potential effective and cost-effective strategies

Strategies to lower morbidity and mortality from alcohol/HIV: Big Picture

Screen at-risk alcohol → Treat at-risk alcohol

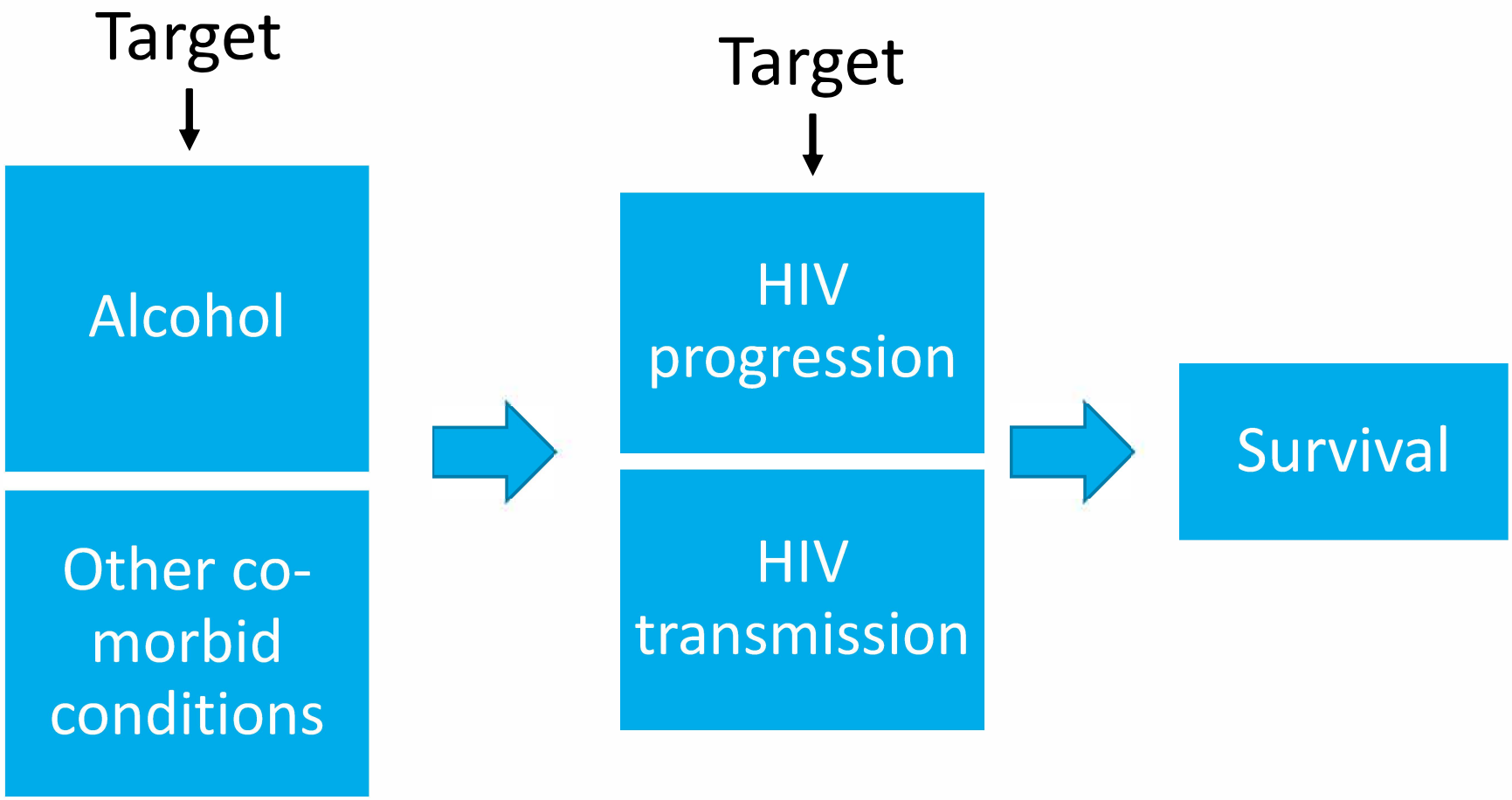
Screen at-risk alcohol → Screen/treat ADAPTOS*

Screen at-risk alcohol → Lower transmission risk directly

+/- Preferentially target highest-risk for HIV transmission

*ADAPTOS = **A**t-risk alcohol, **D**epression, **A**nxiety, **P**ain, **T**obacco, **O**pioids, **S**timulants

Strategies to lower morbidity and mortality from alcohol/HIV: Big Picture



Strategies to lower morbidity and mortality from alcohol/HIV: Interdependencies

Interdependence of screening

- One screening may directly address >1 ADAPTOS condition

Interdependence of treatment

- One treatment may directly address >1 ADAPTOS condition
- Amelioration of 1 ADAPTOS condition may ameliorate others

Interdependencies of screening in more detail

At-risk alcohol screening may also detect anxiety, depression, and stimulant use

- Treating 1 may treat others (eg, naltrexone)
- May facilitate patient-centered care
  - Someone may prioritize treating anxiety above reducing alcohol, but both may improve

At-risk alcohol may be marker of importance of reducing HIV risks in other ways

- Reduce viral load
- PrEP

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Alcohol Consumption and Comorbid Conditions

The US Preventive Services Task Force recommends routine screening for alcohol consumption

Alcohol screening conducted as a part of routine primary care potentially can help identify those at heightened risk for these comorbid conditions

Veterans Aging Cohort Study (VACS)

A cohort study of U.S. veterans receiving healthcare within the Veterans Health Administration

HIV-infected and age/race/site matched HIV-uninfected controls

Aims to understand the role of comorbid alcohol-related medical and psychiatric disease in HIV infection

Includes clinical, administrative, and survey data

Alcohol Use Severity Assessment

Alcohol Use Disorders Identification Test (AUDIT)

- 10-item questionnaire
- Score range: 0-40
  - <8 (low risk)
  - 8-15 (hazardous)
  - 16-19 (harmful)
  - ≥20 (dependent)

AUDIT-C

- First 3 AUDIT items
- Score range: 0-12
  - <4 (low risk)
  - 4-5 (hazardous)
  - 6-7 (harmful)
  - ≥8 (dependent)

Domains	Question Number	Item Content
Hazardous Alcohol Use	1	Frequency of drinking
	2	Typical quantity
	3	Frequency of heavy drinking
Dependence Symptoms	4	Impaired control over drinking
	5	Increased salience of drinking
	6	Morning drinking
Harmful Alcohol Use	7	Guilt after drinking
	8	Blackouts
	9	Alcohol-related injuries
	10	Others concerned about drinking

Babor, WHO

Statistical Analyses

Odds ratios and 95% confidence intervals (CIs) for associations between categories of alcohol consumption severity and co-morbid factors

Likelihood ratios to assess test characteristics of alcohol consumption severity categories using AUDIT and AUDIT-C for the detection of co-morbid conditions

- Sensitivity/(1-Specificity)
- Does test result usefully change the odds that a condition exists?

Results

	DEPRESSION	ANXIETY	MODERATE PAIN
Full AUDIT	**Odds Ratio (95% CI)**		
<8 (Abstinence/ Low Risk)	Referent		
8-15 (Hazardous)	1.96 (1.61 – 2.36)	2.16 (1.79 – 2.60)	1.14 (0.96 – 1.36)
16-19 (Harmful)	3.98 (2.74 – 5.78)	2.67 (1.82 – 3.90)	2.26 (1.60 – 3.19)
20-40 (Possible Dependence)	8.66 (6.39 – 11.72)	9.38 (6.67 – 13.2)	2.89 (2.17 – 3.85)

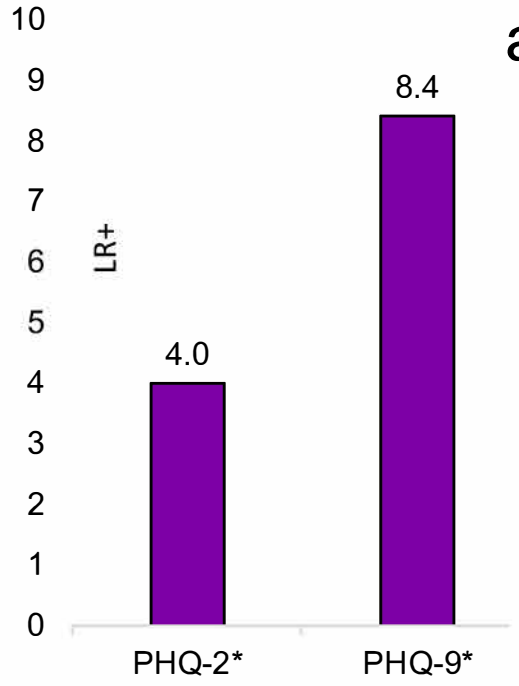
Results

	TOBACCO	MARIJUANA /HASHISH	CRACK/ COCAINE	STIMULANTS	OPIOIDS (NMUPO OR HEROIN)	INJECTION DRUG USE
Full AUDIT	**Odds Ratio (95% CI)**					
<8 (Abst/ Low Risk)	Referent					
8-15 (Hazardous)	4.95 (3.67 – 6.69)	2.96 (2.35 – 3.72)	6.28 (4.96 – 7.94)	4.12 (2.69 – 6.33)	1.56 (1.29 – 1.90)	2.54 (1.74 – 3.73)
16-19 (Harmful)	4.20 (2.32 – 7.60)	5.20 (3.36 – 8.05)	10.08 (6.45– 15.75)	3.30 (1.44 – 7.61)	2.65 (1.83 – 3.82)	2.40 (1.15 – 5.02)
20-40 (Possible Dependence)	16.14 (9.81 –26.54)	8.68 (5.98– 12.61)	31.48 (21.6- 45.81)	20.31 (12.0– 34.38)	3.21 (2.41 – 4.27)	9.30 (5.66 - 15.25)

Results

Pre-test probability of depression=20%
Pre-test odds = .2 / (1-.2) = 0.25
LR=3.0
Post-test odds = 0.25*3=0.75
Post-test probability of depression=.75/(1+0.75)=43%

Likelihood ratio values of the PHQ-2, PHQ-9, AUDIT, and AUDIT-C for detection of depression



*Compared to Composite International Diagnostic Interview (CIDI) criteria for depression

**Compared to a score of 10 or greater on the PHQ-9

Results

Likelihood ratio values of the GAD-7, AUDIT, and AUDIT-C for detection of anxiety

*Compared to DSM-5 criteria for generalized anxiety disorder

**Compared to self-report of past month anxiety

Implications

First analysis to assess the value of using AUDIT and AUDIT-C for detection of other conditions

Alcohol consumption screening may identify populations at elevated risk of comorbid conditions

- Higher cutoffs strongly correlated with other conditions
- Even lower cutoffs demonstrate correlation

AUDIT has greater information signal compared with AUDIT-C and improved case finding effectiveness

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Motivation

At-risk alcohol, depression, anxiety, pain, tobacco, opioids, stimulants co-occur and predict one another

- Association or causation?

Can targeting one condition reduce the risk of developing another condition?

Can targeting one condition help to treat another condition?

Example – reducing unhealthy alcohol consumption

What is the effect of reducing unhealthy alcohol consumption

- On the continuation of other comorbid conditions?
- On the development of other comorbid conditions?

Example: Among smokers, what is the effect of reducing unhealthy alcohol consumption on quitting smoking?

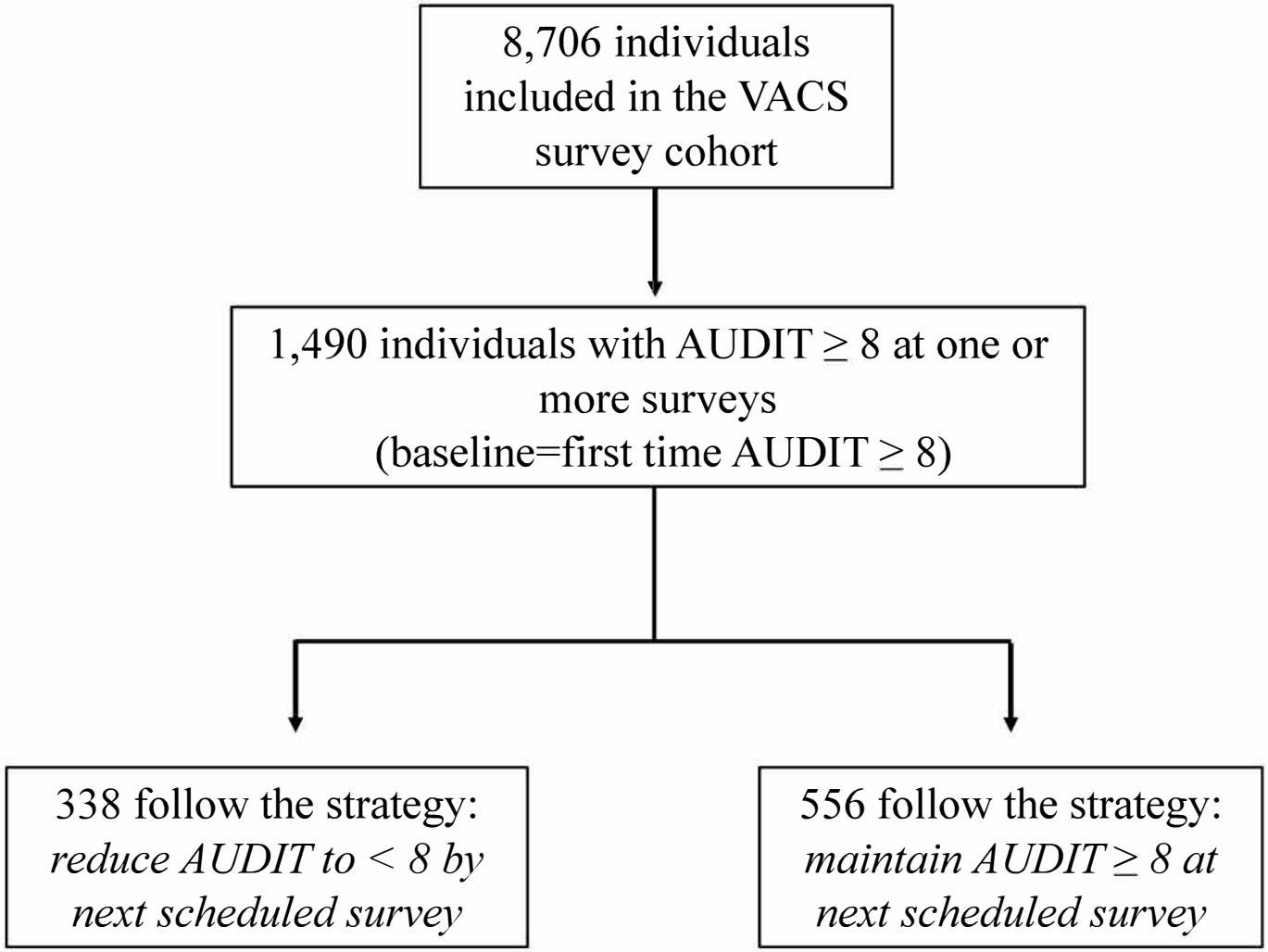
Hypothetical (target) randomized trial of reducing alcohol consumption

Study component	Target trial protocol
Eligibility criteria	AUDIT ≥ 8 at trial enrollment (randomization)
Treatment strategies	1. Reduce AUDIT to < 8 within the next 12 months 2. Maintain AUDIT ≥ 8 over the next 12 months
Start of follow-up	Randomization
Outcome	Status of each co-morbid condition at 1 and 2 years after baseline
Analysis Plan	Logistic regression models for each outcome at 1 and 2 years

Emulating target trial using VACS observational data

Study component	Target trial protocol	Target trial emulation
Eligibility criteria	AUDIT ≥ 8 at trial enrollment (randomization)	Same
Treatment strategies	1. Reduce AUDIT to < 8 within the next 12 months 2. Maintain AUDIT ≥ 8 over the next 12 months	1. Reduce AUDIT to < 8 ***by next survey*** 2. Maintain AUDIT ≥ 8 ***by next survey***
Start of follow-up	Randomization	First time AUDIT ≥ 8
Outcome	Status of each co-morbid condition at 1 and 2 years after baseline	Status of each co-morbid condition at next two surveys
Analysis Plan	Logistic regression models for each outcome at 1 and 2 years	Same, but use inverse probability weighting to adjust for confounding

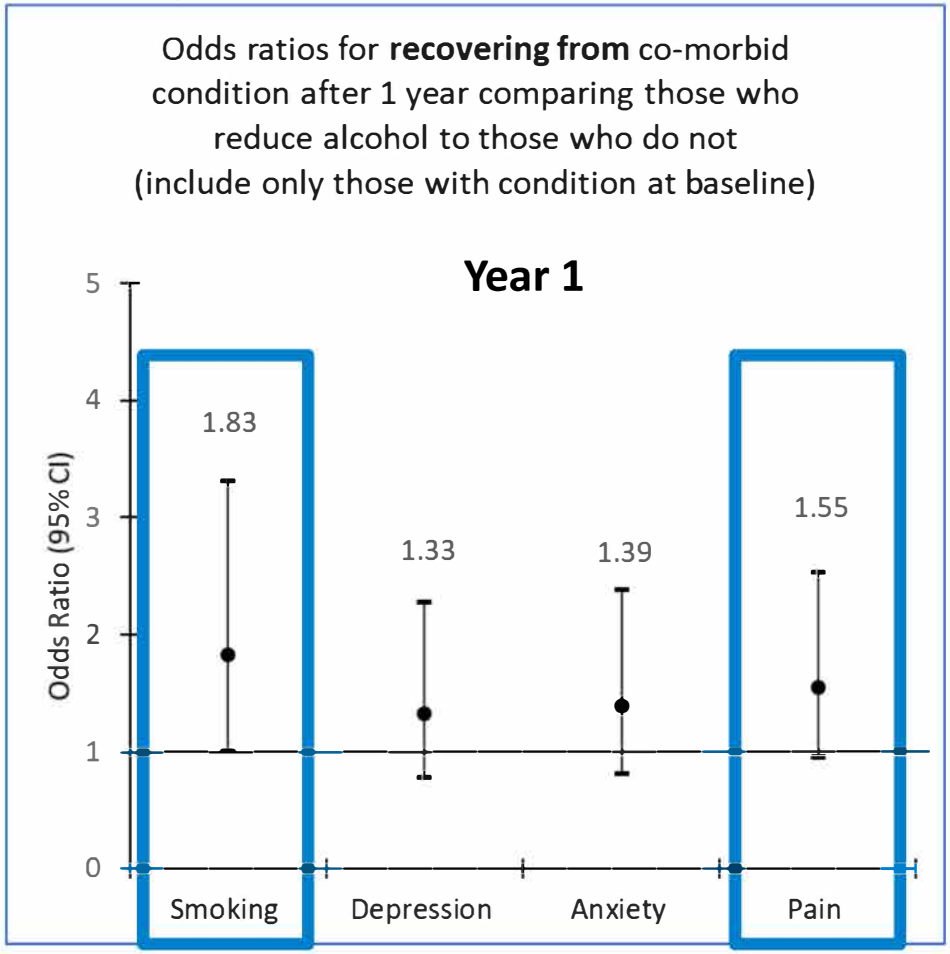
Study schema



Baseline characteristics (n=1,490)

Male	98%
HIV-infected	49%
African-American	71%
High school education or more	89%
Household income <$12,000	55%
Current depression	33%
Current anxiety	54%
Chronic pain	45%
Current smoker	68%
Past year marijuana use	34%
Past year cocaine use	34%
Past year stimulant use	6%
Past year NMUPO or heroin	4%

Results (preliminary)- reducing alcohol and recovering from co-morbid condition



Adjusted for baseline AUDIT, smoking, depression, anxiety, pain, marijuana, cocaine, stimulant, opioid, HIV status, sex, race, education, and income.

Potential implications

Target trial emulation can compare various treatment and screening/monitoring strategies

Results can inform guidelines and future interventions

Reducing unhealthy alcohol consumption may increase the odds of resolving smoking and pain

“Reduce unhealthy alcohol consumption” only one example

- Others include “quit smoking” or “treat depression”

Limitations of observational data

Sample size

- Can only evaluate strategies that a sufficient number of people follow in the real world
- Difficult to evaluate complex, time-varying, combination strategies

Data quality

- Can only evaluate exposures and outcomes that are measured in the data
- Difficult to evaluate ART adherence, cause of death, longer term outcomes

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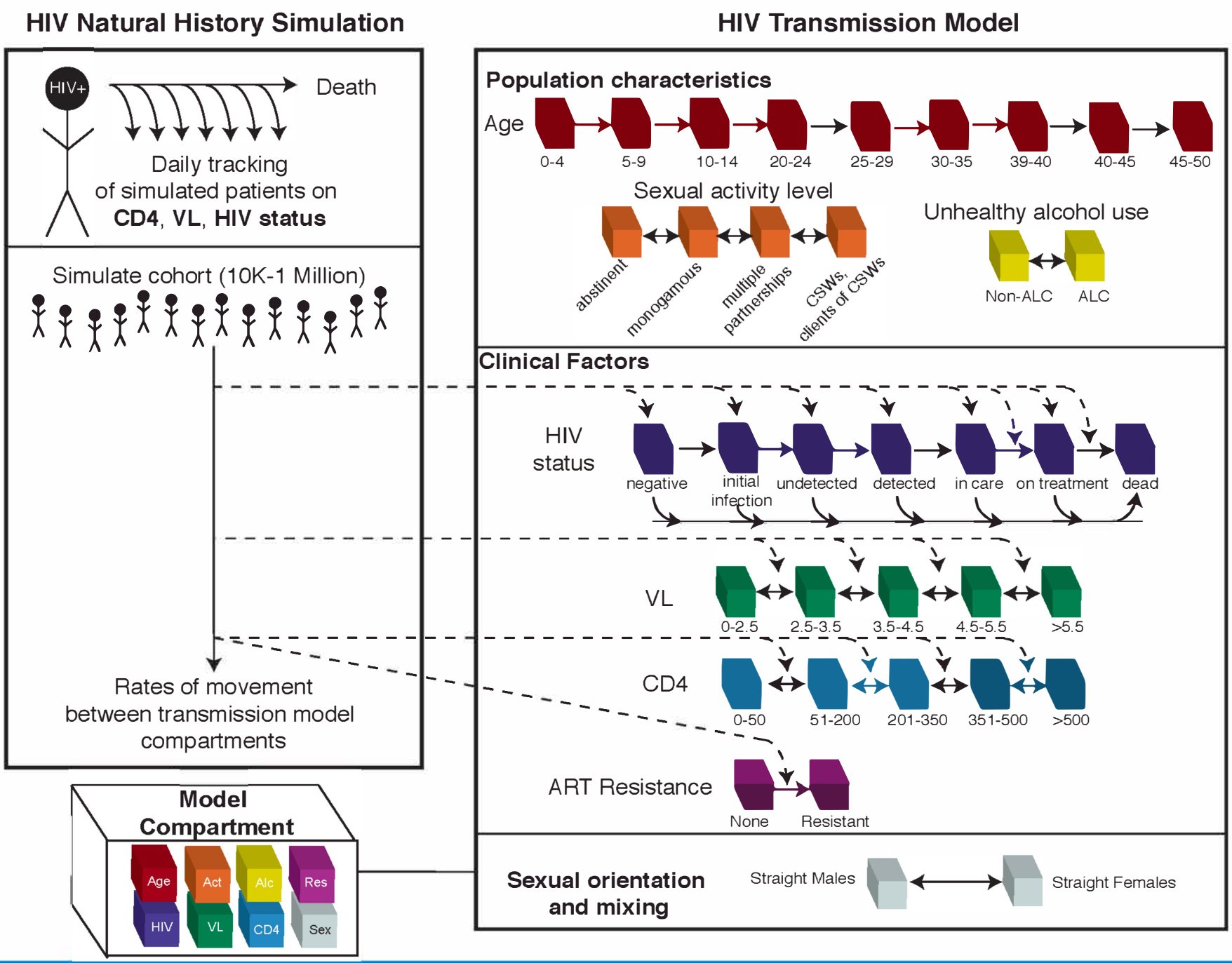
Answering complex questions using mathematical modeling

Computer simulations can be useful to model the effects of unhealthy alcohol consumption on HIV outcomes

- Optimize combination interventions
- Allocate resources efficiently

Uses existing health literature and primary data sources to obtain model inputs

Extensive calibration and validation process


HIV Natural History Simulation
HIV Transmission Model
HIV+
Death
Daily tracking
of simulated patients on
CD4, VL, HIV status
Simulate cohort (10K-1 Million)
Rates of movement
between transmission model
compartments
Model
Compartment
Age
Act
Alc
Res
HIV
VL
CD4
Sex
Population characteristics
Age
0-4
5-9
10-14
20-24
25-29
30-35
39-40
40-45
45-50
Sexual activity level
abstinent
monogamous
multiple
partnerships
CSWs,
clients of CSWs
Unhealthy alcohol use
Non-ALC
ALC
Clinical Factors
HIV
status
negative
initial
infection
undetected
detected
in care
on treatment
dead
VL
0-2.5
2.5-3.5
3.5-4.5
4.5-5.5
>5.5
CD4
0-50
51-200
201-350
351-500
>500
ART Resistance
None
Resistant
Sexual orientation
and mixing
Straight Males
Straight Females

Computer simulation of alcohol and HIV - example

Computer simulation of the Kenyan population over 20 years

Integrating transmission and progression model

Model estimated the effects of behaviors accompanying **unhealthy alcohol consumption** responsible for **13% of new HIV infections in Kenya**

- Through condom use, ART adherence, and STI prevalence

An **alcohol intervention** that yields a 45% reduction in unhealthy alcohol consumption* **could prevent nearly half of HIV infections** and reduce mortality by 2.3%

Braithwaite et al. *Alcohol Clin Exp Res*. 2014.
Papas et al. *Addiction*. 2011. Papes et al. *AIDS Behav*. 2010.

Computer simulation to inform guideline development

Intervention	Conditions addressed	May be favored in
Topiramate	Alcohol consumption Smoking	Cocaine users
Varenicline	Alcohol consumption Smoking	
Naltrexone+Antidepressants+CBT	Alcohol consumption Depression	Smokers
Antidepressant+Alcohol reduction treatment	Depression	Alcohol dependence
Antidepressant+Substance use treatment	Depression Cocaine use	
Nicotine replacement therapy + CBT	Alcohol dependence Smoking Depression	Alcohol dependent smokers

Modeling alternative strategies

Persons

- AUDIT or AUDIT-C as initial screener
- AUDIT or AUDIT-C + other ADAPTOS screeners
- Transmission risk as initial screener

Intervention

- Alcohol-focused: brief intervention or pharmacotherapy
- ADAPTOS-focused
- Transmission risk-focused: viral load reduction or PrEP

Outcomes

- LY, QALY, infections averted
- Alcohol-related infections averted, alcohol-related LYs, alcohol-related QALYs

Modeling alternative scenarios

Patient

- Not interested in treating/modifying anything
- Only interested in treating/modifying some ADAPTOS conditions
- Interested in treating/modifying everything

Health system

- Offers all ADAPTOS-related services at same place/time
- Offers all services but not at same place and/or same time
- Only offers some services

Criteria for evaluating alternative strategies

Incremental cost effectiveness ratio (ICER)

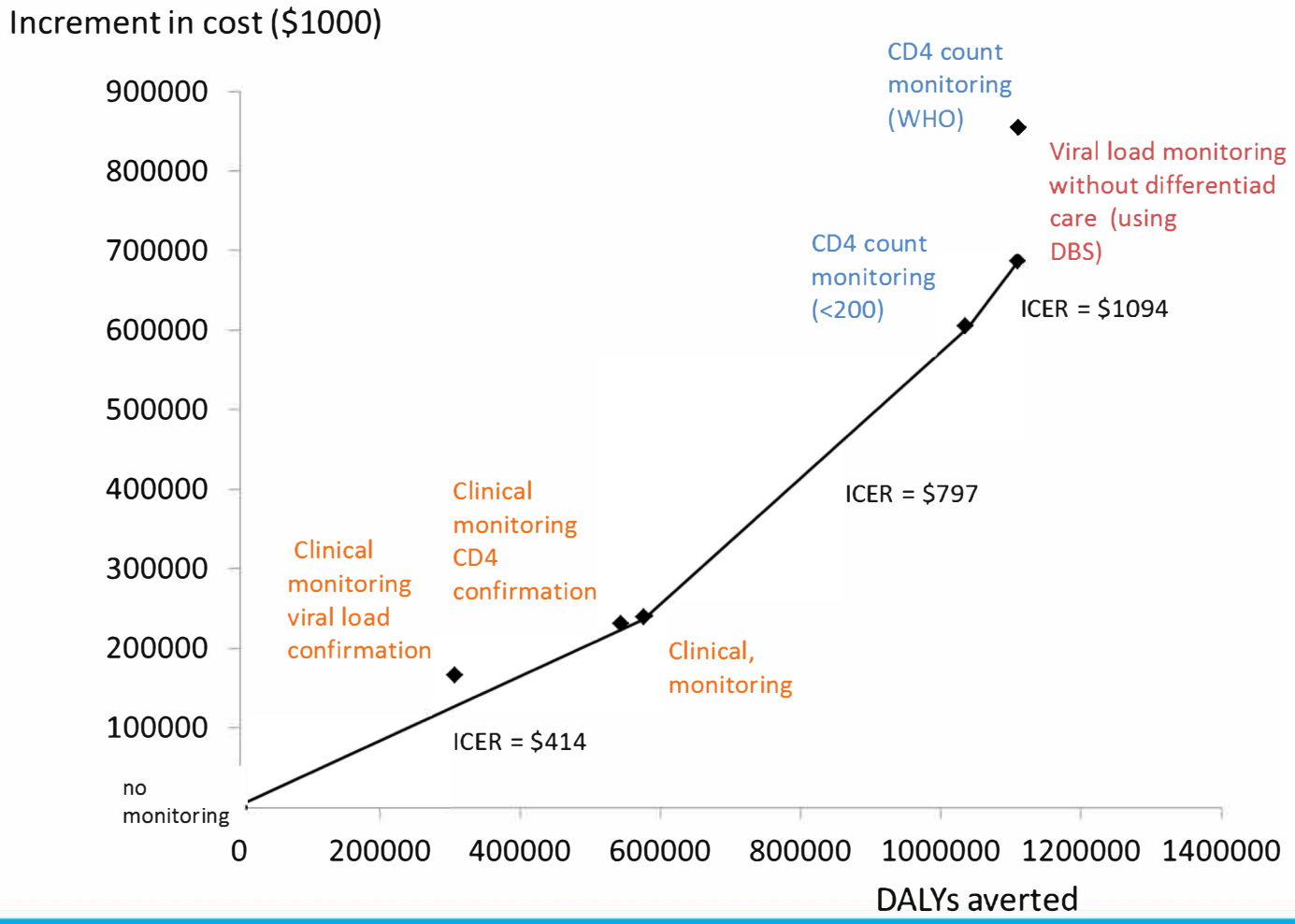
- Cost per additional life year gained compared with previous best option
- Want ICER ≤ opportunity cost for simultaneously resource constrained activities

Efficient frontier

- Strategies delivering the greatest health benefit given a particular budget

Incremental benefit has significance for population health

Sample Result: Efficient Frontier



Summary

Alcohol should be conceptualized with other co-morbid conditions in HIV prevention and treatment

Observational data can identify potentially effective screening strategies and emulate hypothetical randomized trials

Simulation modeling can identify optimal screening/treatment strategies given resource constraints

Ideally, combine inferences from computer simulation, observational data, and clinical trials to inform guidelines

Thank you!

Questions?

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