Improved inference for vaccine-induced immune responses via shape-constrained methods

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Joint work with

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(b) Ying Huang  
(c) Alex Luedtke

Section 1

Background
AIDS and vaccination

- HIV-1 is the most common strain of the virus.
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- **Effective slow-down of HIV-1 infection:** vaccine efficacy $\geq 50\%$ is desirable. (Medlock *et al.*, 2017).

Vaccine efficacy

Vaccine efficacy is the percentage reduction of the disease in a vaccinated group of people compared to the Placebo group.
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The RV 144 Trial

RV 144 vaccine (ALVAC-HIV vector + AIDSVAX B/E) trial showed 31% efficacy against HIV-1 (Rerks-Ngarm et al., 2009).

1 Image source: IChemE
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HIV vaccine trials

RV 144

Phase III, Conducted in Thailand
The estimated efficacy of the vaccine regimen is 31%

HVTN 097
Phase 1b, Conducted in South Africa
Evaluated the safety and immune profile of RV 144 regimen in the new demography
Vaccine efficacy was still less than 50%, so researchers wanted modification!
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Modifications

- Clade C prevalent clade in South Africa
- RV144 efficacy decreased after the first year
**Modifications**

- Clade C prevalent clade in South Africa
- Replace the clade B/E inserts in RV 144/ HVTN 097 regimen with clade C inserts
- RV144 efficacy decreased after the first year
- Booster added after the first year.
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- Phase 2b/3, finished in June 2021 in South Africa
- Uses HVTN 100 regimen, estimated efficacy 0.
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Comparison between the designs of HVTN 097 and HVTN 100 trials

HVTN 097
- Conducted in South Africa
- Placebo controlled, randomized, double blind
- Age range: 18-40
- Male : female ∼ 9:7 (per protocol)

HVTN 100
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Key immune correlate: IgG antibody binding to HIV envelope

Studies (Rolland and Gilbert, 2012; Haynes et al., 2012) indicate that the binding of IgG antibody to the V1V2 region of glycoprotein (gp) 120 of HIV envelope may be associated with blocking the HIV-1 infection.

(a) Envelope of HIV virus

(b) IgG antibody

1 Image source: dreamstime.com
Our aim

- How does the modification in the HVTN 100 regimen change the IgG binding?
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- Estimate the density of the IgG binding magnitude in both trials – may help in future vaccine development.
IgG binding rate in our trials
### IgG binding rate in our trials

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Quantifying the immune response

We consider only the positive respondents for this study.

The magnitude of the IgG binding responses is measured in net MFI (mean fluorescence intensity) units. Variable of interest: log(net MFI).

We consider the aggregated immune responses corresponding to seven clade C antigens.
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Subsection 1

Some exploratory Analysis
Histogram and KDE

(a) Histograms of the immune responses

(b) KDEs of the immune responses
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Histogram and KDE

(a) Histograms of the immune responses

(b) KDEs of the immune responses
Questions

Question 1
Will considering a unimodal density estimator improve the density estimation?
Shape-constrained estimation: advantage

Nonparametric and shape-constrained estimators have similar large sample guarantees in many cases but ....
Figure: KDEs (with Gaussian kernels) calculated from a sample of 100 standard Gaussian random variables. The true density is drawn in black dotted line. The optimal tuning parameter may vary depending on the context.
Shape-constrained estimation: advantage

- Little to no dependence on external tuning. Implementation does not require domain knowledge!
- Shape-constrained estimators may have better finite sample performance. Phase 1b trials are small/moderate sized.
Figure: Boxplot of the immune responses from the trials HVTN 097 and HVTN 100
Empirical distribution functions of the immune responses from the trials HVTN 097 and HVTN 100
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Are the immune responses of the HVTN 097 trial higher than that of the HVTN 100 trial?
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Question 3: If the answer to Question 2 is “yes”, how can we measure the difference?
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Density estimation
Shape-constrained density estimation

- The real advantage: Small shape-constrained class (e.g., monotone densities) \(\rightarrow\) log-likelihood can be exactly maximized \(\rightarrow\) the MLE exists.
Shape-constrained density estimation

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- Easier implementation, tuning parameter free estimation, good theoretical properties
The class of all unimodal densities

This class is too large to admit an MLE. (Birgé, 1997).
Unimodal density estimation

- Birgé (1997)'s estimator depends on one truncation parameter $\eta$. If $\eta \sim 1/n$, estimator not much sensitive on the choice of $\eta$.
Mode known $\Rightarrow$ MLE exists (Rao, 1969) – the Grenander estimate.
Unimodal density estimation

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Figure: Plot of different unimodal density estimators for a standard Gaussian sample of size $n = 100$. The true density is drawn in black dotted line.
Subsection 1

Log-concave densities
Log-concave densities

- Subclass of unimodal densities.

- Many commonly used unimodal densities are log-concave, e.g. Gaussian, Beta, Gamma distribution with shape parameter greater than 1, Laplace, logistic, Gumbel etc.

- Structurally rich =⇒ MLE exists tuning parameter free, easily computable, no domain knowledge needed.
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Example of log-concave densities

Figure: Plot of standard Laplace, logistic, and normal density
Log-concave MLE

Concave affine function (Dümbgen and Rufibach, 2009).

Smoothed version (Chen and Samworth, 2013): data-dependent smoothing.

Figure: Log-concave MLEs based on a sample of 100 standard Gaussian observations. The true density in black dotted line.
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**Figure:** Log-concave MLEs based on a sample of 100 standard Gaussian observations. The true density in black dotted line.
Testing the null of log-concavity (Chen and Samworth, 2016)

P-values were 0.4890 and 0.4631 for HVTN 097 and HVTN 100, respectively.
Subsection 2

Density estimation for the immune responses
Density estimation

Compute the density estimators for the immune responses from both trials.

Perform a ten fold cross validation to estimate the mean integrated square error (MISE) of each density.
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The density estimators

Density estimators

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Log-concave

KDE

Birge (1997), Turnbull and Ghosh (2014)
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(a) The log-concave MLE
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Question 2

Are the immune responses of the HVTN 097 trial higher than that of the HVTN 100 trial?
A more precise question

Are the immune responses from the HVTN 097 trial stochastically larger than that of HVTN 100?
Stochastic dominance (first order)

- $X \sim F$ and $Y \sim G$. $F \geq_{st} G$, i.e. $X$ (or $F$) stochastically dominates $Y$ (or $G$) if $F(x) \leq G(x)$, for all $x \in \mathbb{R}$.

The dominance is "strict" (we say $F >_{st} G$), if there exists $x \in \mathbb{R}$, such that $F(x) < G(x)$. 

![Graph showing stochastic dominance between functions F and G](image)
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![Graph showing stochastic dominance](image-url)
Section 3

Test of stochastic dominance
Testing stochastic dominance

Want to test the null of non-dominance ($G \preceq_{st} F$) against the alternative of strict stochastic dominance ($G <_{st} F$).

Rejection of this test makes the strongest case for ranking $F$ over $G$. 
Testing stochastic dominance

- Want to test the null of non-dominance ($G \not\succ_{st} F$) against the alternative of strict stochastic dominance ($G \prec_{st} F$).
Testing stochastic dominance

- Want to test the null of non-dominance ($G \not\geq_{st} F$) against the alternative of strict stochastic dominance ($G <_{st} F$).
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Non-dominance of $F$ over $G$
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$F$ does not strictly stochastically dominate $G$ ($G \not\prec_{st} F$).
Non-dominance of $F$ over $G$

$F$ does not strictly stochastically dominate $G$ ($G \not\prec_{st} F$).
Caution! Two distribution functions always overlap at the tails

Rejection of the null of non-dominance is difficult (Davidson and Duclos, 2013; Álvarez-Esteban et al., 2016; Whang, 2019)

Here $F \sim \text{Gamma}(2, 1)$, a gamma distribution with shape parameter 2 and scale parameter 1, and $G$ is the standard exponential distribution function.
Remedy: Restricted stochastic dominance

\[ F \sim \text{Gamma}(2, 1) \] and \( G \) is the standard exponential distribution function.
Restricted stochastic dominance (Davidson and Duclos, 2000)

Our $H_1$ and $H_0$

$C$: compact subset of the combined support.

$H_1$: $F(x) < G(x)$ for all $x \in C$.

$H_0$: the above does not hold.
Notations and preliminaries

\[ X_1, \ldots, X_m \sim f \quad \text{and} \quad Y_1, \ldots, Y_n \sim g. \]

\[ F \quad \text{and} \quad G \quad : \quad \text{Distribution functions corresponding to} \quad f \quad \text{and} \quad g. \]

\[ H \quad : \quad N = m + n. \]

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<td>$X_1, \ldots, X_m, Y_1, \ldots, Y_n$</td>
</tr>
</tbody>
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Choice of the constrained set $C$

Fix $p \in (0, 1/2)$. We take the restricted set $C$ in $H_{0}$ to be $[H_{-1}N(p), H_{-1}N(1-p)]$.

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Existing Methods:

▶ Kaur et al. (1994)'s method rejects the test for large values of $\inf z \in D_{p,m,n}$

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- Nonparametric empirical likelihood method (Davidson and Duclos, 2013).
Our test statistics
Our test statistics

\( \hat{F} \) and \( \hat{G} \): some estimators of \( F \) and \( G \).
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- Minimum t-statistic (MT):

\[
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- **Two sample empirical process (TSEP):**

\[
T_2(\hat{F}, \hat{G}) = \sqrt{\frac{mn}{N}} \inf_{z \in [\rho, 1-\rho]} \frac{\hat{G}(\mathbb{H}_{N}^{-1}(z)) - \hat{F}(\mathbb{H}_{N}^{-1}(z))}{\sqrt{z(1-z)}}.
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\]

Choice of \((\hat{F}, \hat{G})\): **NP** (ECDF), **UM** (the CDF of Birge’s estimators), **LC** (the CDF of LC MLEs).
Our test statistics
Subsection 1

Asymptotic critical values
Our test statistics

- Test statistics
  - MT
    - NP
    - UM
    - LC
  - TSEP
    - NP
    - UM
    - LC
Our test statistics

Test statistics

MT
- NP
- UM
- LC

TSEP
- NP
- UM
- LC
Regulatory conditions

- $F$ and $G$ have continuous densities $f$ and $g$. 

As $m, n \to \infty$, $m/N \to \lambda \in (0, 1)$. (1)
Regulatory conditions

- $F$ and $G$ have continuous densities $f$ and $g$.
- As $m, n \to \infty$,
  \[ m/N \to \lambda \in (0, 1). \]  \hspace{1cm} (1)
Asymptotic critical values of the nonparametric tests

$Z_\alpha$: $(1 - \alpha)$th quantile of $N(0, 1)$ distribution

**Theorem (Davidson and Duclos, 2000; Kaur et al., 1994)**

With the critical value $Z_\alpha$, the NP MT test

- has asymptotic power one at all alternatives.
- controls asymptotic type I error at all null-configurations.

**Theorem (Laha et al., 2021)**

With the critical value $Z_\alpha$, the NP TSEP test

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**Result for unimodal (UM) tests (Laha et al., 2021)**

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<th>Curvature condition</th>
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<td>The Lebesgue measure of the sets, where $f$ or $g$ is positive, but flat, is 0.</td>
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\[ f(x) \]

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Curvature condition

The Lebesgue measure of the sets, where $f$ or $g$ is positive, but flat, is 0.

This condition + unimodality $\implies$ Asymptotic critical values for UM tests: $Z_\alpha$. 
Result for log-concave (LC) tests (Laha et al., 2021)

Curvature condition

Neither $\log f$ nor $\log g$ are affine on any interval inside their respective supports.

This condition + log-concavity $\implies$ Asymptotic critical values for LC tests: $Z_\alpha$. 
Subsection 2

Simulation
Simulation: general set-up

$m = n = 100$.

$p$ of $D_p$, $m$, $n$ is 0.05.

Estimate the power from 10000 Monte Carlo samples.
Simulation: general set-up

- \( m = n = 100 \).
Simulation: general set-up

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Choosing $F$ and $G$
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- We generate observations from $(F_\gamma, G_\gamma)$, where $\gamma$ varies between zero and one.
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- We generate observations from $(F_\gamma, G_\gamma)$, where $\gamma$ varies between zero and one.
- $\nu(\gamma)$: power corresponding to the configuration $(F_\gamma, G_\gamma)$.
Case (a): null of equity

\[ F_\gamma \sim N(\gamma, 1), \quad G_\gamma \sim N(0, 1). \]
Case (b): crossing

\[ F_\gamma \sim N(3\gamma, 1), \text{ and } G_\gamma \sim N(0.5, 2). \]

\[ x_\gamma = 0.33 \quad G_\gamma \quad F_\gamma \]
\[ x_\gamma = 0.5 \quad G_\gamma \quad F_\gamma \]
\[ x_\gamma = 0.6 \quad G_\gamma \quad F_\gamma \]
\[ x_\gamma = 0.7 \quad G_\gamma \quad F_\gamma \]
\[ x_\gamma = 0.83 \quad G_\gamma \quad F_\gamma \]
\[ x_\gamma = 1 \quad G_\gamma \quad F_\gamma \]

*Gamma*(a, b) is a Gamma random variable with shape parameter a and scale parameter b.
Case (c): crossing

\( F_\gamma \sim \text{Gamma}(2, 0.1 + 0.4\gamma) \) and \( G_\gamma \sim \text{Gamma}(1, 0.5) \).

\[
\begin{align*}
\gamma &= 0 \\
G_\gamma &\quad F_\gamma \\
\gamma &= 0.25 \\
G_\gamma &\quad F_\gamma \\
\gamma &= 0.5 \\
G_\gamma &\quad F_\gamma \\
\gamma &= 0.55 \\
G_\gamma &\quad F_\gamma \\
\gamma &= 0.62 \\
G_\gamma &\quad F_\gamma \\
\gamma &= 1 \\
G_\gamma &\quad F_\gamma
\end{align*}
\]
Plot of the power-curve: $\nu(\gamma) \text{ vs } \gamma$

**Figure:** The black horizontal line corresponds to level 0.05, and the black vertical line corresponds to the least favorable $\gamma$, 0.70 (middle) and 0.55 (right).
Plot of the power-curve: $\nu(\gamma)$ vs $\gamma$

Figure: The black horizontal line corresponds to level 0.05, and the black vertical line corresponds to the least favorable $\gamma$, 0.70 (middle) and 0.55 (right).

LC tests have the highest power!
Case (d): only log-concavity violated

\( F_\gamma \sim \text{Gamma}(2, 1) \) and \( G_\gamma \sim \text{Pareto}(0.5 + 2\gamma, 1) \).

Here \( \text{Pareto}(a, b) \) is the Pareto distribution function with shape parameter \( a \) and scale parameter \( b \).
Case (e): log-concavity and unimodality both violated

\[ F_\gamma \sim N(0, 1) \text{ and } G_\gamma \sim N(2\gamma + 4, 1)/2 + N(2\gamma - 2, 1)/2. \]
Plot of the power-curve: $\nu(\gamma)$ vs $\gamma$

**Figure**: The black horizontal line corresponds to level 0.05, and the vertical line corresponds to the least favorable $\gamma$, 0.65 (left) and 0.80 (right).
Plot of the power-curve: $\nu(\gamma)$ vs $\gamma$

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TSEP shape-constraint tests do not perform much worse than nonparametric tests.
Subsection 3

Application to our data
The p-values of our tests

<table>
<thead>
<tr>
<th>Test</th>
<th>MT</th>
<th>TSEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>0.026</td>
<td>0.045</td>
</tr>
<tr>
<td>LC</td>
<td>0.014</td>
<td>0.035</td>
</tr>
<tr>
<td>UM</td>
<td>0.031</td>
<td>0.037</td>
</tr>
</tbody>
</table>

We take $p = 0.075$ in $D_{p,m,n}$. 
Questions

Question 1: Will considering a unimodal or log-concave density estimator improve the density estimation?

Question 2: Are the immune responses of the HVTN 097 trial higher than that of the HVTN 100 trial?

Question 3: If the answer to Question 2 is “yes”, how can we measure the difference?
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Section 4

Measure of discrepancy between two densities
Hellinger distance

Hellinger distance $H^2(f, g)$ between densities $f$ and $g$:

$$H^2(f, g) = \frac{1}{2} \int_{-\infty}^{\infty} \left( \sqrt{f(x)} - \sqrt{g(x)} \right)^2 dx.$$
Hellinger distance

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- Plug-in or bias-corrected estimators.

- **Shape-constrained estimator of Hellinger distance**: simpler estimator? better performance?
Plug-in estimators of $H^2(f, g)$
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Estimator

- Shape-constrained
- KDE: non-parametric

Unimodal
Plug-in estimators of $H^2(f, g)$

Estimator

- Shape-constrained
  - Unimodal
  - Log-concave

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Plug-in estimators of $H^2(f, g)$

- Shape-constrained
  - Unimodal
  - Log-concave
  - Smoothed log-concave
- KDE: non-parametric
Plug-in estimators of $H^2(f, g)$

Estimator

Shape-constrained

Unimodal

Log-concave

KDE: non-parametric

Naive

Smoothed log-concave
Estimators of $H^2(f, g)$

- **Shape-constrained**
  - Unimodal
  - Log-concave
  - Smoothed log-concave

- **KDE: non-parametric**
  - Naive
  - Bias-corrected
Asymptotic properties of the unimodal plug-in estimators:

<table>
<thead>
<tr>
<th>Theorem 3 of Laha et al. (2021) [rough]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppose $f$ and $g$ are unimodal. Then under conditions, the centered and scaled (by $\sqrt{N}$) unimodal plug-in estimator is asymptotically normal with variance $\sigma_{f,g}^2$ depending on $\lambda$, $f$ and $g$. Here $N = m + n$</td>
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Under log-concavity, both log-concave estimators are strongly consistent. We conjecture (based on simulations) that under log-concavity + mild conditions, a result like Theorem 3 holds for the log-concave plug-in estimators.
Asymptotic properties of the KDE-based estimators:

- Under conditions (Kandasamy et al., 2015), the bias-corrected KDE estimator has same asymptotics as the unimodal plug-in estimator.
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- Under conditions (Kandasamy et al., 2015), the bias-corrected KDE estimator has the same asymptotics as the unimodal plug-in estimator.
- Under conditions, the KDE estimator has a $O_p(N^{-2/5})$ bias term for smooth $f$ and $g$ (Robins et al., 2009).
Subsection 1

Simulation
Common set-up

- Set $m = n$ and consider $n = 50, 100, 150, \ldots, 500$.
- 10000 Monte Carlo samples.
Setting 1: location shift

\[ f \sim N(1, 1), \ g \sim N(0, 1) \]

Method
- UM
- LC
- KDE
- KDE(BC)
- Smoothed LC

Scaled MSE (by n)

Coverage

\[ n \]
Setting 2: Different density families

\( f \sim N(0, 1), \) and \( g \sim Gamma(3.61, 1.41) \)

<table>
<thead>
<tr>
<th>Method</th>
<th>UM</th>
<th>LC</th>
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</table>

**Scaled MSE (by n)**

**Coverage**

\( n \)
Setting 3: Violation of shape-constraints

\( f \sim N(0, 1), \text{ and } g \sim \frac{[N(6, 1) + N(0, 1)]}{2} \)

<table>
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<th>Method</th>
<th>UM</th>
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**Scaled MSE (by n)**

**Coverage**
Application to our data

<table>
<thead>
<tr>
<th>Estimator</th>
<th>Point estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDE</td>
<td>0.16</td>
<td>–</td>
</tr>
<tr>
<td>KDE (BC)</td>
<td>0.19</td>
<td>(0.110, 0.274)</td>
</tr>
<tr>
<td>UM</td>
<td>0.21</td>
<td>(0.128, 0.300)</td>
</tr>
<tr>
<td>LC</td>
<td>0.18</td>
<td>(0.098, 0.256)</td>
</tr>
<tr>
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<td>0.15</td>
<td>(0.079, 0.228)</td>
</tr>
</tbody>
</table>
Section 5

Conclusion
HIV vaccine trials

RV 144
- Phase III, conducted in Thailand
- The estimated efficacy of the vaccine regimen is 31%

HVTN 097
- Phase 1b, conducted in South Africa
- Evaluated the safety and immune profile of RV 144 regimen in the new demography

HVTN 100
- Phase 1/2, conducted in South Africa
- Modified the RV 144 (HVTN 097) regimen, added more Clade C antigens

HVTN 702
- Phase III, conducted in South Africa
- Uses HVTN 100 regimen, efficacy 0%
Implication:

- RV 144 trial (HVTN 097 regimen) has significantly higher efficacy than HVTN 702 trial (HVTN 100 regimen).
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- RV 144 trial (HVTN 097 regimen) has significantly higher efficacy than HVTN 702 trial (HVTN 100 regimen).
- Our findings indicate that HVTN 100 regimen induces significantly lower IgG binding.

IgG binding to V1V2 region of HIV envelope is associated with the prevention of HIV-1 infection. The decrease in IgG binding may be connected to the failure of HVTN 702 trial (HVTN 100 regimen).
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From a broader perspective

▶ In homogeneous populations, log-concave density estimators may improve density estimation in moderate sized samples.
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- Shape-constrained plug in estimators of Hellinger distance: Smooth log-concave estimators outperform nonparametric estimators when the shape constraint is satisfied. They neither require tuning nor the extra step of bias correction.
Thank you


