Evaluating the Impact of Timing of Therapy on Tuberculosis Risk in HIV Patients

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HIV

- As of 2017, roughly 36.9 million individuals around the world are infected with HIV that causes AIDS.
- According to WHO, 1.1 million people died from AIDS in 2016.
- At the beginning of the HIV/AIDS epidemic, most HIV infected individuals died within 10 years of infection.

ART Therapy

- HIV attacks the immune system's **CD4** cells causing those infected with HIV to be much more susceptible to disease(s).
- While HIV has no cure, ART is recommended to help control the severity of the virus.
- ART helps with...
  - Suppressing viruses and diseases
  - Rebuilding the immune system
  - Reducing HIV associated complications

HIV in Haiti

- About 150,000 people in Haiti have HIV/AIDS.
- Only 55% of those people received ART treatment.
- Haiti also has limited resources to help those with HIV.
  - In accordance with the WHO guideline, ART treatment doesn't begin until after CD4 counts fall below 200 cells/mm^3.


SO YOU THINK 200 CELLS/MM^3 IS A GOOD CUTOFF HUH?


WHO saying you should receive treatment after your CD4 cell count falls below 200 cells/mm^3
Us:

CIPRA HT-001 Study

- This study tried to investigate whether the WHO guideline is sufficient or not.
- 773 subjects from Haiti had baseline CD4 counts between 200 and 350 cells/mm^3.
- They were randomly assigned to two ART treatment groups:
  - Standard (delayed) group: Subjects initiated treatment according to the WHO guideline
  - Early group: Subjects received ART at enrollment of study

Tuberculosis

- The clinical end-point of this study is incidence of tuberculosis (TB).
- The symptoms used to identify TB in this study were fever, night sweats, weight loss, cough, dyspnea, hemoptysis, and lymphadenopathy.
- Final diagnosis were confirmed if *M. tuberculosis* culture was positive.
- Population of interest: Individuals in Haiti with HIV that received antiretroviral therapy (ART) during study and didn't have tuberculosis at baseline.

Delayed Vs. Early Analysis

We ran a **logistic regression model** to compare the incidence of tuberculosis between delayed and early groups.

$$\widehat{logit(Y)} = \widehat{\beta_0} + \widehat{\beta_1} * Delay$$

Y is 1 if patient has TB; 0 if not
Delay is 1 if patient is in delayed group; 0 if in early group.

	Parameter Estimate	Z-Value	Pr(>|z|)		Odds Ratio
Intercept	-2.457	-12.91	2e-16	***	
Delay	0.954	4.05	5.17e-5	***	2.597

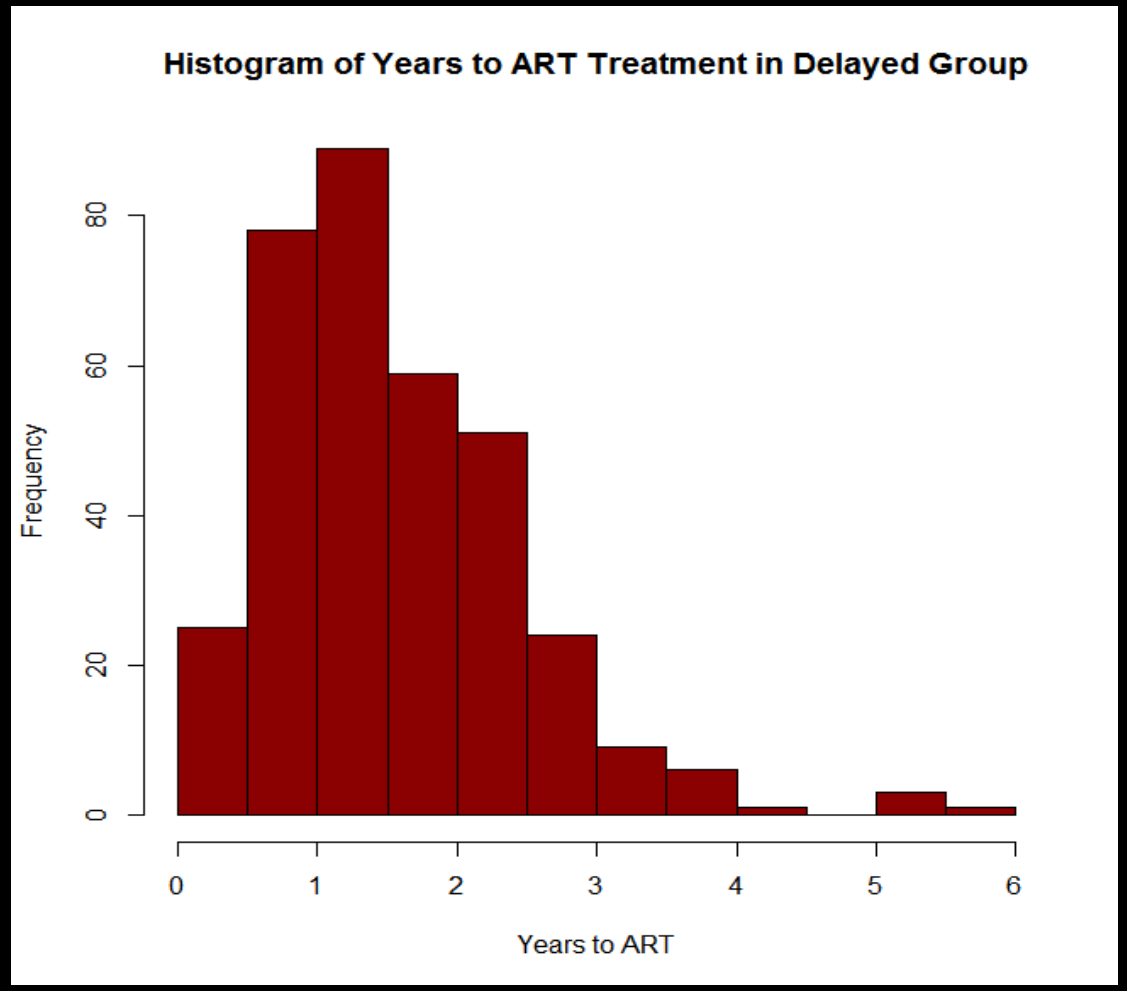
With the estimated odds of 2.597, individuals are more susceptible to contracting tuberculosis in the delayed group.

Evaluate the Impact of Timing of ART Initiation

- Timing of ART depends on the guideline.
- Investigate whether timing of ART initiation is associated with TB incidence.
- We conducted the subgrouping analyses in the delayed group.

Design of Subgroups

- Based on the median cutoff we made two groups
  - More delayed group(greater than 1.33)
  - Less delayed group (less than or equal to 1.33)



Based on the WHO guidelines, the median year to ART is 1.33 years

Comparison of Subgroups

More Delayed Vs. Early

$$\widehat{logit(Y)} = \hat{\beta}_0 + \hat{\beta}_1 * Moredelay$$

	Parameter Estimate	Z-Value	Pr(>|z|)	Odds Ratio
Intercept	-2.456	-12.910	2e-16 ***	
MoreDelayed	1.042	3.860	0.0001 ***	2.833

Less Delayed Vs. Early

$$\widehat{logit(Y)} = \hat{\beta}_0 + \hat{\beta}_1 * Lessdelay$$

	Parameter Estimate	Z-Value	Pr(>|z|)	Odds Ratio
Intercept	-2.457	-12.910	2e-16***	
LessDelayed	0.861	3.090	0.002***	2.366

Both odds ratios are greater than 1.

1<OR(Less Delayed) < OR(Delayed Vs. Early) < OR(More Delayed)

2.3660 < 2.5971 < 2.8334

Characterization of Patients between Less Delayed and More Delayed Group

$$\widehat{logit(Y)} = \widehat{\beta_0} + \widehat{\beta_1} * Sex + \widehat{\beta_2} * Age + \widehat{\beta_3} * BMI + \widehat{\beta_4} * Hemoglobin + \widehat{\beta_5} * CD4 + \widehat{\beta_6} * PPD\ Test$$

Y = 1 if subject is in More Delayed subgroup Y = 0 if patient is in Less Delayed subgroup

The predictors are:

- Sex (1 if male, 0 if female)
- Age (years)
- BMI (kg/m^2)
- Hemoglobin(g/dl)
- CD4 ($cells/mm^3$)
- PPD Test (1 if patient received PPD test, 0 if not)

The Result of Analyses: Comparing More and Less Delayed

	Parameter Estimate	Z-Value	Pr(>|z|)
Intercept	-6.414	-4.347	0.00001 ***
Sex	0.225	0.837	0.4027
Age	0.003	0.223	0.8237
BMI	-0.033	-0.977	0.3285
Hemoglobin	0.312	3.739	0.0001 ***
CD4	0.012	3.724	0.0002 ***
PPD Test	-0.052	-0.214	0.8305

Conclusion

- Delayed therapy increases the odds of contracting tuberculosis
- Subgrouping into More and Less Delayed
- Higher CD4 and hemoglobin at baseline means more delayed treatment.
- Healthier individuals are at greater risk of contracting tuberculosis.
- Based on our analyses, we can conclude that WHO guideline can play a different role depending on the individual.

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