Cohort Studies

Vincent Lo Re, MD, MSCE, FISPE
Department of Medicine (Infectious Diseases)
Center for Pharmacoepidemiology Research and Training
Perelman School of Medicine
University of Pennsylvania

4th MURIA – June 18, 2018

CPeRT Center for Pharmacoepidemiology Research and Training

ISPE

Learning Objectives

- Learn strengths, limitations of cohort study design
- Understand measures of disease frequency and effect from cohort design
- Recognize cohort design in literature

Outline: Cohort Studies

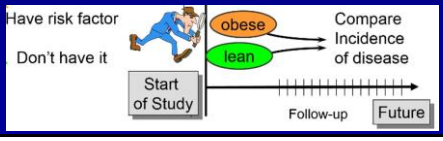
- Definition, overview
- Advantages, disadvantages
- Analysis
- Examples

Outline: Cohort Studies

- Definition, overview
- Advantages, disadvantages
- Analysis
- Examples

Definition of a Cohort Study

- Study which selects patients on the basis of the presence or absence of exposure to a factor of interest
- Follows patients through time to determine their outcome(s)



Options in Research Design

Descriptive Studies

- Case reports
- Case series
- Analysis of secular trends

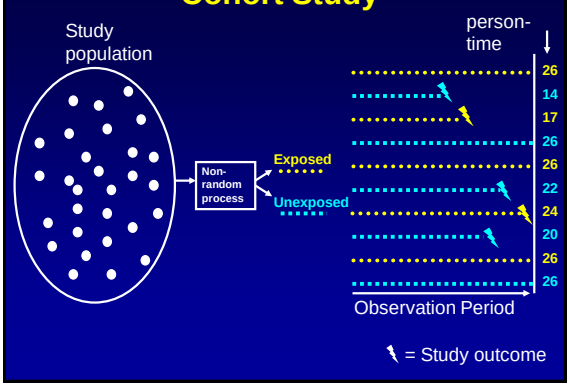
Analytic Studies

- Case-control
- Retrospective cohort
- Prospective cohort
- Experimental

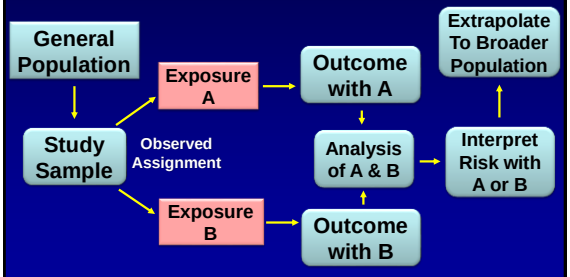
Cohort Study

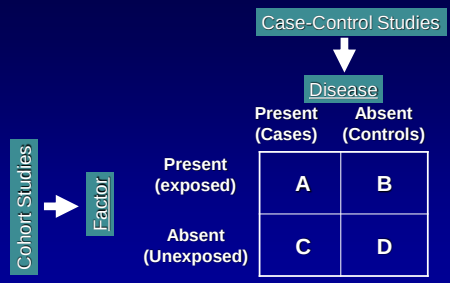
- **Definition**
  - Compares patients with risk factor/exposure to others without for differences in outcome
- **Use**
  - Study any number of outcomes from singly risk factor/exposure
- **Main limitation**
  - Prolonged, costly

Cohort Study

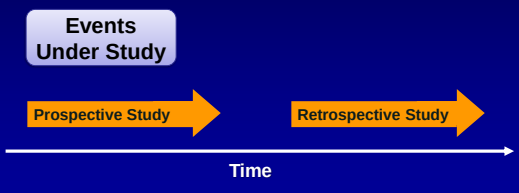


Cohort Study





Retrospective vs. Prospective Studies



Outline: Cohort Studies

- Definition, overview
- Advantages, disadvantages
- Analysis
- Examples

Trade-Offs in Research Design

- Informativeness
  1. Internal validity
  2. External validity (generalizability)
- Feasibility

Cohort Study Design

Advantages

- Calculate incidence
- Study many outcomes
- Outcome unknown at study start
- Intuitive

Disadvantages

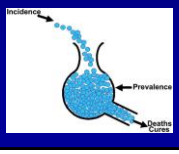
- Large sample size needed for rare dz
- Long follow-up required
  - Loss to follow-up
  - Changes over time in criteria, methods
  - Costly

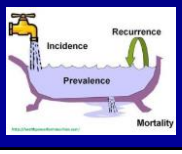
Outline: Cohort Studies

- Definition, overview
- Advantages, disadvantages
- Analysis
- Examples

Prevalence

$$\text{Prevalence} = \frac{\text{No. of } \textit{existing cases} \text{ of disease at a } \textit{specified point in time}}{\text{No. of people in the population at that time}}$$





Incidence

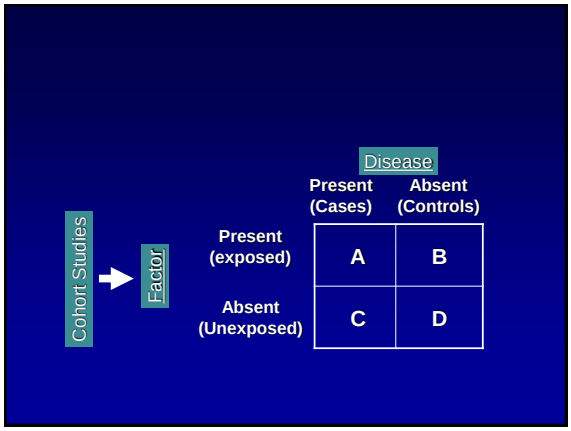
$$\text{Incidence} = \frac{\text{No. of } \textit{new cases} \text{ of disease over a period of time}}{\text{No. of people } \textit{at risk} \text{ of developing the disease during that time}}$$

- May want to calculate person-time of follow-up
- Account for different entry, dropout rates → varying duration of follow-up

Attributable Risk

- Absolute difference in incidence between exposed and unexposed groups

$$\text{Attributable Risk} = \text{Incidence}_{\text{exposed}} - \text{Incidence}_{\text{unexposed}}$$



Cohort Studies: Calculation of Relative Risk

	Cohort Size	# Developing Disease
Exposed	A+B	A
Unexposed	C+D	C

$$\text{Risk of Disease Among Exposed} = \frac{A}{(A+B)}$$

$$\text{Risk of Disease Among Unexposed} = \frac{C}{(C+D)}$$

$$\text{Relative Risk (Risk Ratio)} = \frac{\left(\frac{A}{A+B}\right)}{\left(\frac{C}{C+D}\right)}$$

Relative Risk

$$\text{Relative Risk (RR)} = \frac{\text{Incidence of Outcome in Exposed}}{\text{Incidence of Outcome in Unexposed}}$$

- RR > 1.0 → Exposure assoc. with outcome
- RR = 1.0 → No relation for exposure, outcome
- RR < 1.0 → Exposure may be protective

Calculation of Analytic Measures in Cohort Study: Example

- Perform cohort study examining risk of acute kidney injury with tenofovir in HIV

Exposure	Outcome: AKI	Outcome: No AKI	
Tenofovir	10	40	50
No Tenofovir	15	135	150
			200

Calculation of Analytic Measures in Cohort Study: Example

Exposure	Outcome: AKI	Outcome: No AKI	
Tenofovir	10	40	50
No Tenofovir	15	135	150
			200

$$RR = \frac{\text{Incidence}_{\text{Exposed}}}{\text{Incidence}_{\text{Unexposed}}} = \frac{10/50}{15/150} = 2.0$$

$$\text{Attributable Risk} = \text{Incidence}_{\text{Exposed}} - \text{Incidence}_{\text{Unexposed}} = 0.1$$

Cohort Studies: Calculation of Incidence Rate Ratios

	Person-Time At Risk	# Developing Disease
Exposed	T_1	A
Unexposed	T_0	C

$$\text{Incidence Rate Among Exposed} = \frac{A}{T_1}$$

$$\text{Incidence Rate Among Unexposed} = \frac{C}{T_0}$$

$$\text{Incidence Rate Ratio} = \frac{\left(\frac{A}{T_1}\right)}{\left(\frac{C}{T_0}\right)}$$

Outline: Cohort Studies

- Definition, overview
- Advantages, disadvantages
- Analysis
- Examples

EPIDEMIOLOGY AND SOCIAL SCIENCE

Incidence and Risk Factors for Weight Loss During Dual HIV/Hepatitis C Virus Therapy

Vincent Lo Re, III, MD, MSCE,†‡ Jay R. Kostman, MD,* Robert Gross, MD, MSCE,*†‡ K. Rajender Reddy, MD,§ Karam Mounzer, MD,‖ Babette S. Zemel, PhD,¶ Hanna Rennert, PhD,# Donald D. Stieritz, PhD,** Mary Putt, PhD,† Ian Frank, MD,* and Brian L. Strom, MD, MPH†‡*

Background: Clinical observations suggest that patients with HIV/hepatitis C virus (HCV) may lose body weight during dual therapy, but this has not been confirmed analytically.

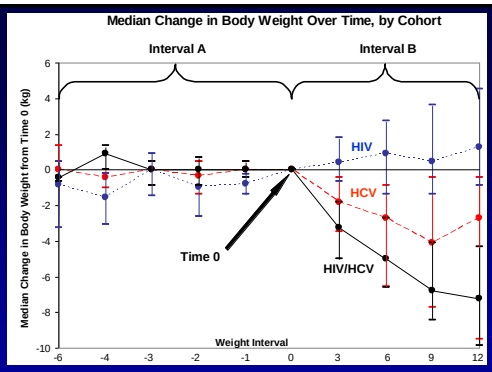
Objectives: To determine if the incidence and degree of weight loss among patients with HIV/HCV receiving highly active antiretroviral therapy (HAART) and pegylated (PEG)-interferon plus ribavirin were greater than in (1) HCV-monoinfected patients receiving PEG-interferon plus ribavirin and (2) HIV-monoinfected patients receiving HAART. Risk factors for weight loss among patients with HIV/HCV were also examined.

Methods: A retrospective cohort study was performed among HIV/HCV-coinfected, HCV-monoinfected, and HIV-monoinfected patients. Body weights were assessed up to 6 months before and up to 12 months after initiation of HCV therapy (HIV/HCV-coinfected and HCV-monoinfected subjects) and over 18 months on HAART (HIV-monoinfected subjects). The primary outcome was clinically significant weight loss (≥5% of baseline weight).

Results: Of 192 subjects, 63 had HIV/HCV, 64 had HCV alone, and 65 had HIV alone. Clinically significant weight loss occurred in 48 (76%) subjects with HIV/HCV versus 25 (39%) subjects with HCV ($P < 0.001$) and 2 (3%) subjects with HIV ($P < 0.001$), yielding adjusted hazard ratios (HRs) of 2.76 (95% confidence interval [CI]: 1.67 to 4.55) and 38.5 (95% CI: 8.5 to 174.7), respectively. Receipt of more than 2 nucleoside reverse transcriptase inhibitors increased the risk of clinically significant weight loss (adjusted HR = 8.17, 95% CI: 2.37 to 28.20).

Conclusions: The incidence of weight loss is greater in dually treated patients with HIV/HCV than in treated HCV- or HIV-monoinfected patients. Prospective studies should evaluate additional risk factors for weight loss and changes in body composition to elucidate the mechanism for this weight loss.

Lo Re V. *JAIDS* 2007;44:344-50.



Results: Incidence of Clinically Significant Weight Loss

Clinically Significant Weight Loss	HIV/HCV-Coinfected (N=63)	HCV-Monoinfected (N=64)	P-Value
No. of Subjects	48	25	<0.001
Percent (95% CI)	76% (65-87%)	39% (27-51%)	<0.001

RR (95% CI) = 1.95 (1.39, 2.73)

Lo Re V. *JAIDS* 2007;44:344-50.

Results: Incidence of Clinically Significant Weight Loss

Clinically Significant Weight Loss	HIV/HCV-Coinfected (N=63)	HIV-Monoinfected (N=64)	P-Value
No. of Subjects	48	2	<0.001
Percent (95% CI)	76% (65-87%)	3% (0-7%%)	<0.001

RR (95% CI) = 24.8 (6.3, 97.6)

Lo Re V. *JAIDS* 2007;44:344-50.

Annals of Internal Medicine | ORIGINAL RESEARCH

Hepatic Decompensation in Antiretroviral-Treated Patients Co-Infected With HIV and Hepatitis C Virus Compared With Hepatitis C Virus–Monoinfected Patients

A Cohort Study

Vincent Lo Re III, MD, MSCE; Michael J. Kallan, MS; Janet P. Tate, ScD; A. Russell Localio, PhD; Joseph K. Lim, MD; Matthew Bidwell Goetz, MD; Marina B. Klein, MD, MS; David Rimland, MD; Maria C. Rodriguez-Barradas, MD; Adeel A. Butt, MD, MS; Cynthia L. Gibert, MD, MS; Sheldon T. Brown, MD; Lesley Park, MPH; Robert Dubrow, MD, PhD; K. Rajender Reddy, MD; Jay R. Kostman, MD; Brian L. Strom, MD, MPH; and Amy C. Justice, MD, PhD

Background: The incidence and determinants of hepatic decompensation have been incompletely examined among patients co-infected with HIV and hepatitis C virus (HCV) in the antiretroviral therapy (ART) era, and few studies have compared outcome rates with those of patients with chronic HCV alone.

Objective: To compare the incidence of hepatic decompensation between antiretroviral-treated patients co-infected with HIV and HCV and HCV-monoinfected patients and to evaluate factors associated with decompensation among co-infected patients receiving ART.

Design: Retrospective cohort study.

Setting: Veterans Health Administration.

Patients: 4280 co-infected patients who initiated ART and 6079 HCV-monoinfected patients receiving care between 1997 and 2010. All patients had detectable HCV RNA and were HCV treatment-naive.

Measurements: Incident hepatic decompensation, determined by diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage.

Results: The incidence of hepatic decompensation was greater among co-infected than monoinfected patients (7.4% vs. 4.8% at 10 years; $P < 0.001$). Compared with HCV-monoinfected patients, co-infected patients had a higher rate of hepatic decompensation (hazard ratio [HR] accounting for competing risks, 1.56 [95% CI, 1.31 to 1.86]). Co-infected patients who maintained HIV RNA levels less than 1000 copies/mL still had higher rates of decompensation than HCV-monoinfected patients (HR, 1.44 [CI, 1.05 to 1.99]). Baseline advanced hepatic fibrosis (FIB-4 score >3.25) (HR, 5.45 [CI, 1.79 to 7.84]), baseline hemoglobin level less than 100 g/L (HR, 2.24 [CI, 1.20 to 4.20]), diabetes mellitus (HR, 1.88 [CI, 1.38 to 2.56]), and nonblack race (HR, 2.12 [CI, 1.65 to 2.72]) were each associated with higher rates of decompensation among co-infected patients.

Limitation: Observational study of predominantly male patients.

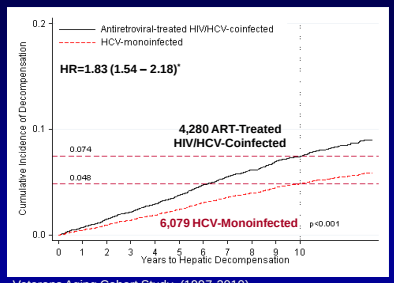
Conclusion: Despite receiving ART, patients co-infected with HIV and HCV had higher rates of hepatic decompensation than HCV-monoinfected patients. Rates of decompensation were higher for co-infected patients with advanced liver fibrosis, severe anemia, diabetes, and nonblack race.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2014;160:369-379. www.annals.org
For author affiliations, see end of text.

Lo Re V. *Ann Intern Med* 2014;160;369-79.

Liver Decompensation Rates are Higher in HIV/HCV vs. HCV Only Patients



Veterans Aging Cohort Study (1997-2010)

* Adjusted for age, race, BMI, alcohol / drug abuse, VA center size.

Lo Re V. *Ann Intern Med* 2014;160;369-79.

Cohort Studies: Key Points

- Selects patients based on exposure
- Can study many outcomes
- Can be retrospective or prospective
- Enables calculation of:
  - Incidence, incidence rate
  - Prevalence
  - Attributable risk