

Overview of Cohort Studies of Stanley H. Weiss, MD: Past and Future April 9, 2019

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THREE MAJOR COHORT STUDIES

- 1) All adults undergoing **colonoscopy** at NJMS over a 2 year period (2,697 colonoscopies) – in 2005-2006
- 2) Participants in any one of the several Stanford “***Take Control of Your Health***” programs we conducted (6 weekly sessions in moderated small groups):
 - I was initially ONLY given short-term funding to enroll ~50 persons
 - There were many claims that these Stanford Programs had already been demonstrated to be efficacious...
 - SHW reviewed the literature, but disagreed → I thus decided to
 - Add multiple medical measure assessments & adjust for therapeutic drugs
 - Submitted IRB protocol as a (potential) large prospective cohort, **despite no apparent prospect of continuation funds**
 - Ultimately we did enroll 642 persons, cobbled from multiple small grants we received to administer these workshops
- 3) Studies of **drug users**...

which will be the focus of the remainder of this talk

THREE MAJOR COHORT STUDIES

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STUDY DESIGN – SOME KEY ISSUES

- 1) Clarify the primary outcomes/issues of interest.

Base this on intensive, critical assessment of the literature: what is known, how well is that already substantiated, what are the limitations of prior studies, what are the priorities

- 2) Define reasonable short, intermediate, and long-term goals.

- 3) Establish multiple secondary outcomes/issues of interest – these can help sustain the study,

Some important, competing issues:

- Size (including power)
- Duration (and types of statistical analyses) and follow-up plans
- Specimen collection?
- Complexity of study protocol and study instruments

SHW's KEY CAVEATS – AND MISTAKES TO AVOID

- **Data is (almost) never missing at random!**
→ Determine procedures and efforts to minimize missing data, and what level of missing data (if any) will be accepted.
- Fully understand the assumptions underlying statistical approaches as well as of the “standard” approaches. ***Do you need to do better?***
- ***Great attention to obtaining accurate data.***
- ***IMHO, quality greatly trumps larger study size.***
- Determine what degree of follow-up is needed, realistically assess resources needed to achieve this, monitor performance, develop procedures to improve as necessary.

Example: CDC study of outcome in HIV+ MSM from a prior HBV vaccine cohort in SF Bay area. Achieved 80% follow-up – a common epidemiologic standard.

Did not follow-up those who had left the area. Was that study design:

1) Adequate?

2) **Likely** to be grossly inadequate?

Summary Background of the Drug User Cohort Studies

- Currently nearly **11,500** enrollments of over **10,300** unique adults, with accumulated person-time since enrollments of $\sim$ **300,000** person-years
- **$\sim$ 100,000 biospecimens (repositories)**
- **Questionnaire data and select lab data**
- **Extensive “locator” data**
- **Follow-up outcomes data**
- **Consent for future research testing and ongoing follow-up**
- ***HOW DID WE GET HERE?***

Early History of the AIDS Epidemic

- **First Report of AIDS.** On **June 5, 1981**, MMWR report of 5 cases of *Pneumocystis carinii* pneumonia (PCP) among previously healthy young men in Los Angeles. These men were described as "homosexuals;" 2 died.
- **July 16, 1982:** CDC MMWR article, "[Epidemiologic Notes and Reports *Pneumocystis carinii* Pneumonia among Persons with Hemophilia A.](#)" First report of immunosuppression in patients with [hemophilia](#) who have no other known risk factors for AIDS.
- **Sept 24, 1982:** CDC [uses the term "AIDS"](#) ([Acquired Immune Deficiency Syndrome](#)) for the first time; releases the first [case definition](#) for AIDS: *"A disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease."* [MMWR Morb Mortal Wkly Rep.](#) 1982 Sep 24;31(37):507-8, 513-4. Some details:

Early History of the AIDS Epidemic

Sept 24, 1982 MMWR:

- 75% of **AIDS** cases involved homosexual or bisexual men, among whom the reported prevalence of intravenous **drug abuse** was 12%.
- Among the 20% of heterosexual cases, the prevalence of intravenous **drug abuse** was 60%.
- Reported AIDS cases separated by CDC into [hierarchical] groups based on the following risk factors:
 - homosexual or bisexual males--75%,
 - **intravenous drug abusers** with no history of homosexual activity—13%,
 - Haitians with neither a history of homosexuality or intravenous drug abuse--6%,
 - persons with hemophilia A with no other risk factors--0.3%, and
 - **persons in none of the other groups--5%.**
 - Includes: blood transfusion recipients; others including some women and children

Early History of the AIDS Epidemic

- **January 7, 1983:** CDC reports the first cases of AIDS in women: [Epidemiologic Notes and Reports Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome \(AIDS\) -- New York.](#)
- **September 1983:** *SHW attends closed 2-day meeting of NIH and CDC scientists reviewing all studies & information on AIDS.*
 - *NO study world-wide on drug users.*
 - *CDC encourages SHW to pursue, and to contact the National Institute on Drug Abuse (NIDA), part of ADMAHA, in Rockville MD,*
- **April 23, 1984:** U.S. DHHS Secretary [Margaret Heckler announces](#) that [Dr. Robert Gallo](#) and his colleagues at the [National Cancer Institute](#) have [found the cause of AIDS](#) , a [retrovirus](#) they have labeled HTLV-III. Four papers are published in *Science*.
- **July 13, 1984:** CDC MMWR: [“avoiding injection drug use and reducing needle-sharing should also be effective in preventing transmission of the virus.”](#)

Early History of the AIDS Epidemic

- SHW begins cohort study of drug users in New Jersey in November 1984, with design informed by some not yet published data:
 - **January 1985.** Weiss SH, Goedert JJ, Sarngadharan MG, The AIDS Seroepidemiology Collaborative Working Group, Gallo RC, Blattner WA. **Screening test** for HTLV-III (AIDS agent) antibodies: specificity, sensitivity and applications. The Journal of the American Medical Association 253:221-225, 1985. (Enabled reliable large-scale testing.)
 - **February 1985:** Landesman SH, Ginzburg HM, **Weiss SH**. Special report: The AIDS epidemic. The New England Journal of Medicine 312:521-525, 1985. (*Our understanding that HIV was a chronic infection with substantial latency and growing risks over time. CDC had a greatly contrary past 1986...*)
 - *Wide variation in number of AIDS cases in IDU by geography.*
 - *Cancer outcomes beyond KS...*
- **March 2, 1985:** FDA [licenses the first commercial blood test](#) to detect HIV. Blood banks begin screening the U.S. blood supply. Testing at clinical sites arrives considerably later.

Why the first cohorts were begun?

- Although use of injection drugs was linked to AIDS early on, there were **no** studies in progress in 1984.
- *My first step: might there be any prior studies to build upon to **jump-start** → literature search.*
- In 1981, a case-control study of drug users in Queens had examined soft-tissue infections, and was published in 1982 and 1983.
- I reached the PI, Jose A Giron, MD. He had **stored** residual sera plus had contact information on those 69 subjects. This offered the possibility of learning what had happened over the ensuing 3 years in a region where cases of AIDS were being seen.
- A collaboration was developed to find and re-contact these participants.
- Clearly too small & too limited a study to examine many evolving issues.
- No other studies with any biologic specimens located.
- Fortuitously, **HTLV-II** isolated from an IDU with AIDS from same area of Queens.

Origin of my initial large study

CHOICE OF SITE

- In most of the US, most AIDS cases associated with MSM (Men who had Sex with Men). ***But in NJ, drug use was a prominent risk factor.***
- Capitalized upon established relationships between the NJDOH and the NCI Division where SHW worked.

AIMS

- Initially planned in 1983-early 1984 to examine risk factors associated with AIDS.
- Study delayed and re-configured in light of Gallo's discovery of HIV and our understanding of the epidemiology at NCI.
- Prospective cohort study, additional key design elements
 - 6 cities chosen, variety of types of treatment (10 programs)
 - Sites included substantial proportions of African-Americans and Latino's
 - **Women** in addition to men – **the first large AIDS-era study to include women**
 - Identified limitations of research assays
 - No time limitation to follow-up

Drug User Studies Overall

- Several cohort studies of adults at high HIV risk were developed by Dr. Weiss beginning in the 1980's, involving multiple collaborators and support from the NCI, NIDA, NJDOH:
 - **NCI & NIDA** provided support totaling **in excess of \$20 million**
 - Study in NJ begun in **1984** (N=**1040**), ~40% women; multiple waves of follow-up, and then
 - A large nationwide cohort of IDU building upon those results
 - **NJDOH** provided funding to extend the work begun in 1984, through a series of grants to Dr. Weiss **beginning in 1988**, to **add a comprehensive assessment of additional women** at high risk for HIV (from both drug treatment and primary care clinics)

Background

- *Nationally: 11,084* persons enrolled from 1981-1992, with **10,066 unique** persons (9.2% of enrollments were repeats); **within NJ** alone: ~ **2,250** unique persons
- 300 enrolled 2017-2018- interview, comprehensive consent
- 500 expected to be enrolled in 2019
- All studies used similar initial data collection procedures, including informed consent for follow-up without time restriction
- **Blood samples and questionnaire data were collected**
- Maintenance of **linkage** between **stored biospecimens** (~100,000 vials) and all other data
- Permission for **future research testing** and ongoing follow-up
- (ALSO: There are several other regional studies of IDU by Dr. Weiss not tabulated above)

Current New Initiatives

- Genetic Studies from cryopreserved material, in collaboration with NIDA and RUCDR:
 - **Cells** (or stored, extracted DNA) OR saliva required, since a large amount of high quality DNA is needed
 - Custom Affymetrix Axiom “Smokescreen Genotyping Array”
646,247 markers
 - Addiction-related genes
 - Ancestry-informative
 - Cardiovascular diseases and traits
 - Lung cancer, pulmonary disease and traits
 - **Serum**
 - Illumina DNA array (requires much less nucleic acid), with
1.5 Million SNPs

Cohort Studies Reflect A Time Machine

Analytic Approaches

- 1. Entire cohort**
- 2. Specific outcomes → cases plus matched controls (3:1 or 5:1 quite feasible)**

That is, a nested case-control analysis
Which is EFFICIENT in resource utilization

Outcome Measures

Baseline Data:

Behavioral data, such as drug, alcohol and tobacco use
Infection with agents such as HIV, HTLV-I, HTLV-II, HCV

Prospective Data

- Incident infections
- Mortality outcomes: cancer, end-stage liver disease, AIDS, fatal overdoses, suicide, other acute & chronic diseases
- Incident cancers

Historical Data: Results of past testing

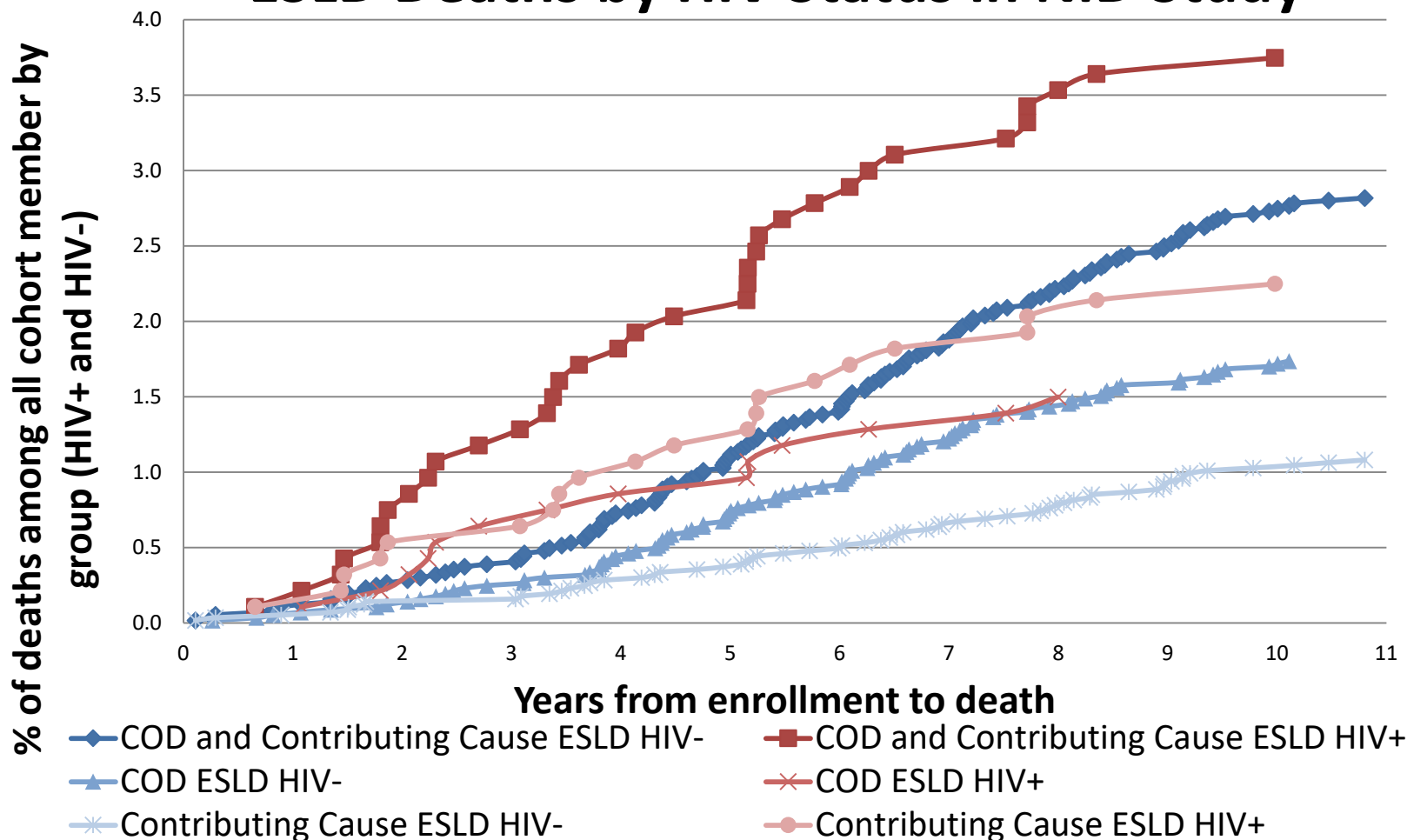
- The **first** systematic testing of Persons Who Injected Drugs (PWID) for **HIV** and **HTLV**; **one of the largest cohorts of HTLV-II infection**
- **HCV** testing of our stored specimens from **NJ** was the **first** demonstration that HCV was extremely common in PWID: **99%** with confirmed antibodies to HCV (Weiss et al., 1995)
- In subset testing of stored blood from NID cohort, **HCV antibodies** were present in >98%,
 - **80%** had detectable HCV **RNA viral titers** using the HCV bDNA version 3.0 (Bayer) test in 2002 ➔ still actively infected,
- <2% were **chronic HBV** carriers (antigen positive), although the majority had antibodies to HBV.
- Using a nested case-control approach, first demonstration that HCV titer at baseline was associated with increased risk of death from liver failure.

Summary: virtually entire cohort HCV +

1. Weiss, S.H.; Skurnick, J.; Zhao, C.; Henrard, D. Mortality due to hepatic failure among a cohort of injection drug users: a preliminary report from the United States. **Anales de Medicina Interna**. 1995. Octubre (suppl.) 57-58.
2. Hisada, M., N. Chatterjee, M. Zhang, R. J. Battjes, and J. J. Goedert. 9-15-**2003**. "Increased Hepatitis C Virus Load Among Injection Drug Users Infected With Human Immunodeficiency Virus and Human T Lymphotropic Virus Type II." **The Journal of Infectious Diseases** 188(6):891-97.

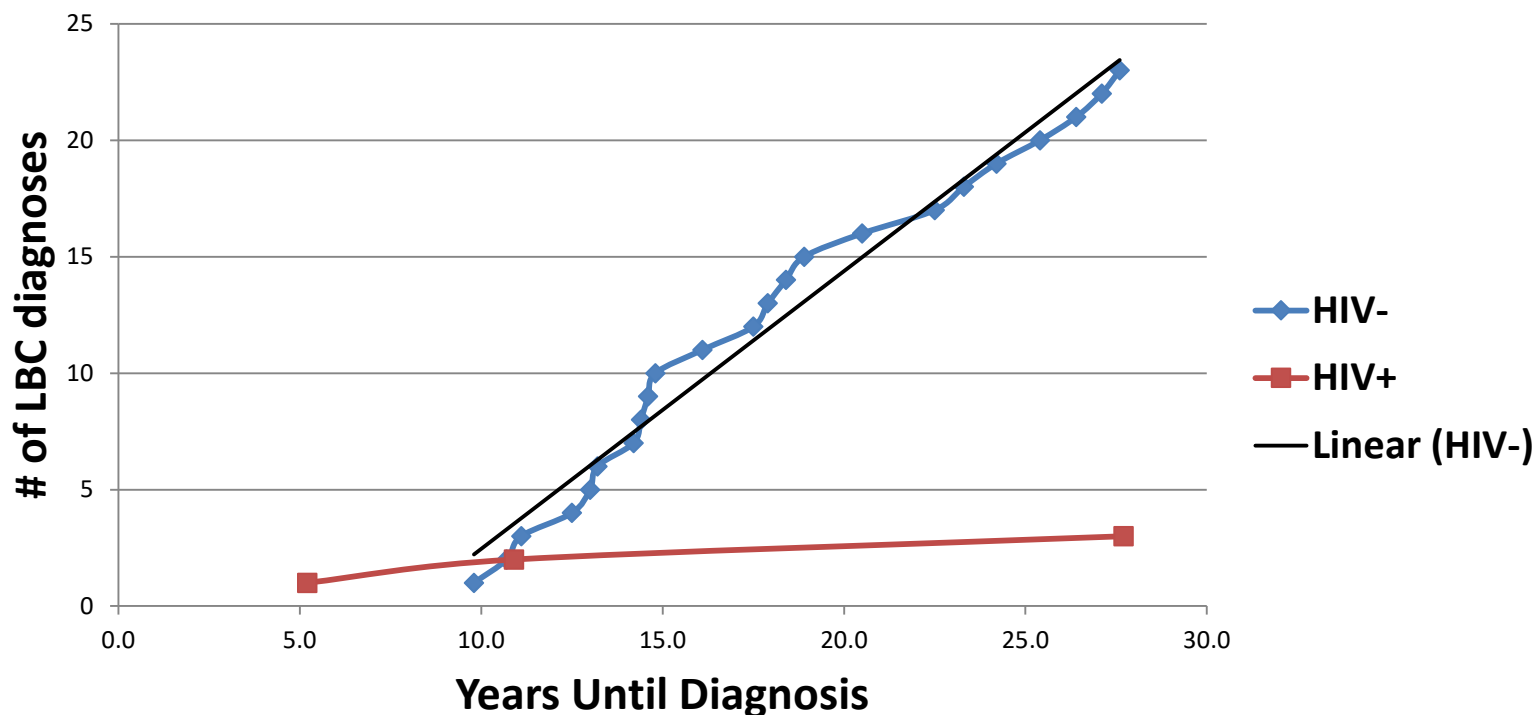
- The percentage of deaths due to ESLD was higher among HIV+ compared to HIV-negative

ESLD Deaths by HIV Status in NID Study



- The first HIV-negative LBC case occurred 9.8 years after enrollment → **LONG LATENCY for this cancer.**
- Thereafter, incidence increased linearly (regression $r^2=0.98$), at a rate of **0.8 LBC per 1000 person-years**
- **UNPUBLISHED DATA (SH Weiss et al.)**

Years from enrollment to diagnosis of liver or biliary cancer (LBC)



Results

Liver Cancer Outcomes (through 2012*): in NJ Subjects

- HIV status available for 2,196 (97.4%); analysis based on:
 - 651 (29.6%) were HIV+ and
 - 1,545 were HIV– (of whom 94 [6.1%] known to have seroconverted)
- The NJSCR linkage helped contribute to our identifying **26** cases of liver (n=25) and biliary cancer (n=1) (**LBC**)
 - 2 in those initially HIV+
 - 3 in HIV seroconverters, and
 - **21 in HIV –**
- LBC risk was significantly **higher** in those **HIV neg** as compared to HIV **pos** (p=0.02, 2-tailed)
- Last match to NJSCR 3 years ago PLUS registry data always 2-3 years behind;
- **New matches in preparation; administrative approvals all granted**