The GSID HIV Data Browser:
A Unique Research Tool Providing Access to AIDSVAX Vaccine Trial Data and Specimens

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GSID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

Global Solutions for Infectious Diseases (GSID)

- Co-founded by former Genentech and VaxGen executives Don Francis, Phil Berman and Carter Lee
- A 501(c)(3) tax exempt public charity
- Mission: apply the newest technologies to develop inexpensive public health tools – vaccines and diagnostics – for less developed countries
- Website: **www.gsid.org**

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Project Goals

- Acquire and disseminate information that will contribute to the development of a safe and effective HIV vaccine
- Establish a consortium to characterize and evaluate antigenic variation of viruses that mediate new infections

GSID Consortium

GENOMA

- Sequence Analysis
- Phylogenetics
- Alignments
  - PI: K. Crandall

GSID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

- Consortium management
- HIV Data Browser
- Specimen repository
  - PI: F. Sinangil

UC SANTA CRUZ

- Bioinformatics
  - PI: J. Kent
- Protein expression and epitope mapping
  - PI: P. Berman

PharmaStat℠
drug development consulting and services

- Biostatistics and clinical data
  - PI: E. Li

monogram biosciences

- Pseudotype virus construction
- Evaluation of neutralization sensitivity
  - PI: B. Schweighardt and T. Wrin

AIDSVAX Phase III Clinical Trials

Design: *Randomized, double-blind, placebo-controlled*	**North America/ Europe VAX004 AIDSVAX B/B**	**Thailand VAX003 AIDSVAX B/E**
rgp120 dose	300 µg (MN)/300 µg (GNE8)	300 µg (MN)/300 µg (A244)
Immunization schedule	0, 1, 6, 12, 18, 24, 30 months	
Transmission	Sexual	Blood borne
# of volunteers	5,400	2,500
Annual Infection rate	1.5%	4.0%
# of clinical sites	59	17
Start date	June 1998	March 1999
Fully enrolled	October 1999	August 2000
Analysis completed	Q1 2003	Q4 2003

VAX003 and VAX004 Results

- No efficacy for prevention of acquisition or for modification of infection detected in the overall trial
- Modification of infection not detected in subgroups, but number of infections may be too small
- Possible efficacy from subgroup analyses despite lack of overall efficacy
  - Blacks or non-whites or women:
    - Differential antibody response
    - Genetic factors
    - Non-genetic factors
  - High-risk volunteers:
    - Priming, analogous to highly uninfected cohorts

Objectives

I. Transfer custodianship of VAX004 and VAX003 data and clinical materials repository from VaxGen to GSID.

   1. Establish a clinical specimen repository.
   2. Establish a web accessible clinical and sequence database.

Specimen Inventory

	VAX004		VAX003		Total
Specimen inventory	Collection Time Points	Sample # (tubes)	Collection Time Points	Sample # (tubes)	Sample # (tubes)
Pre-Infection					
Serum	73,137	135,042	34,484	68,966	**204,008**
Post-infection					
Plasma	2,527	29,282	1,792	15,320	**44,602**
Serum	2,852	2,852	2,171	4,255	**7,107**
Cells	46	2,000	1,783	8,974	**10,974**
Plasmid DNA library					
Full length gp120 plasmids (3 clones per individual sample)		1,050 (350 subjects)		600 (200 subjects)	**1,650**

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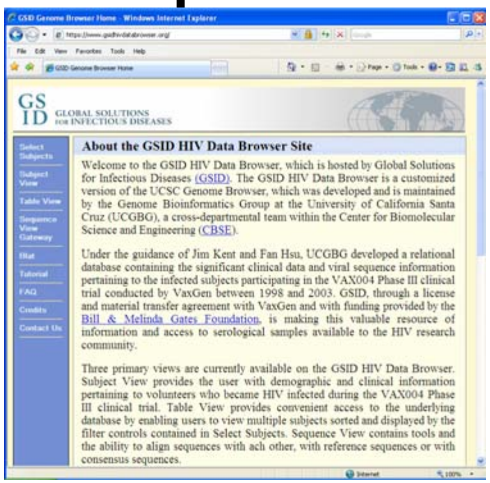
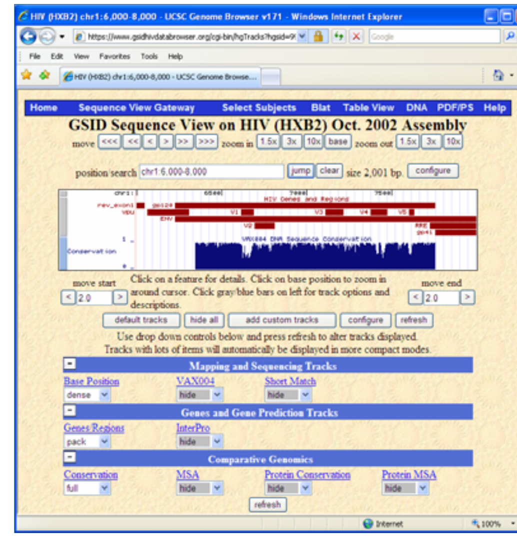
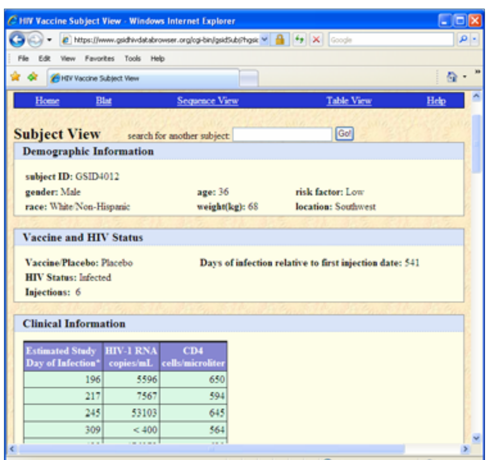
GSID HIV Data Browser

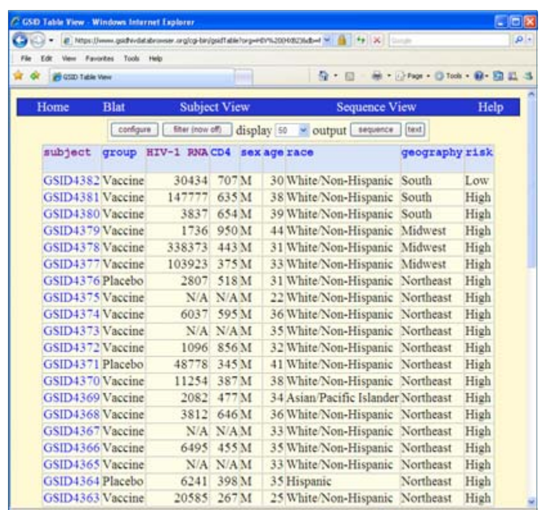
http://www.gsidhivdatabrowser.org

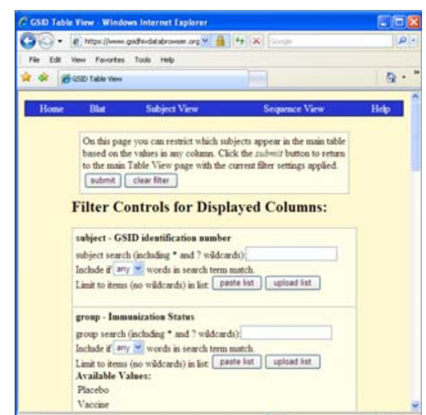


- A Unique Research Tool Providing Access to AIDSVAX Trial Data and Specimens









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Objectives cont.

II. Continued molecular sequence and phylogenetic analyses of viruses and virus envelope proteins obtained close to the time of transmission.

1. Cloning and sequencing of transmission viruses' envelope genes.
2. Sequence analysis of transmission viruses.
3. Structural analysis of transmission viruses
4. Phylogenetic and evolutionary analyses of transmission viruses.
5. Transmission virus database construction and integration with clinical database.

GSID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

GSID Consortium: Genoma LLC

- **VAX004**
  - HIV genetic diversity remains high even with lower infection rates
  - No significant differences in genetic diversity, recombination rates, or levels of selection between vaccinated and placebo patients, gender, geographic region
    - Significant difference in levels of selection between blacks and whites ($P = 0.023$)
- **VAX003**
  - 185 subtype A/E individuals and 34 subtype B′ individuals
  - Substitution rates higher in A/E than in B′
  - No significant differences in genetic diversity, substitution rates or selection between placebo and vaccinated individuals
  - Significantly lower recombination rates in vaccinated individuals compared to placebo

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Objectives cont.

III. Isolation and characterization of broadly neutralizing antibodies to HIV.

1. Phenosense™ virus neutralization assay.
2. Construction of pseudotype viruses and evaluation of neutralizing sensitivity.
3. Identification and characterization of broadly neutralizing antibodies.
4. Biochemical characterization of VAX004 & VAX003 cross neutralizing sera.

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GSID Consortium: Monogram Biosciences

- Developed a new strategy to define important antigenic regions within HIV-1 gp160
- Utilized the newly available resource of early transmission viruses from the VAX004 trial
- Developed and sequenced a library of functional gp160 clones that differ in neutralization sensitivity to heterologous plasma
- Identifying amino acid changes that are associated with shifts in neutralization sensitivity

B. Schweighardt: Genotypic and Phenotypic Characterization of HIV-1 Envelope Clones Isolated from Subjects Infected During the VAX004 Clinical Trials – Dec. 4, Session 7b: Antibody, 4:30 – 6 PM

GSID Consortium: Biomolecular Engineering , UCSC

- **Establish panels of envelope glycoproteins, antisera, and pseudotype viruses from envelope glycoproteins of most representative isolates**
  - Bioinformatics and structural analysis to select panel of representative isolates from VAX003 and VAX004, and characterize most common polymorphisms at neutralizing sites
  - Clone and express gp160 genes from panels of representative isolates
  - Establish panel of pseudotype viruses of representative isolates for neutralization studies (collaboration with Monogram Biosciences)
  - Production of antiserum to purified envelope proteins from representative isolates (gp120 and gp160)

GSID Consortium: Biomolecular Engineering , UCSC

- **Use intra-patient variation in envelope proteins from new infections to characterize epitopes recognized by broadly neutralizing antibodies in HIV+ serum**
  - Compare clones from same individual to identify differences in neutralization sensitivity
  - Characterize minimal sequence differences leading to susceptibility or resistance to virus neutralization
  - In vitro mutagenesis to map sensitivity and resistance to neutralization to single amino acid changes
  - Characterize molecular basis for evolution of neutralization resistance in longitudinal specimens

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http://www.gsidhivdatabrowser.org

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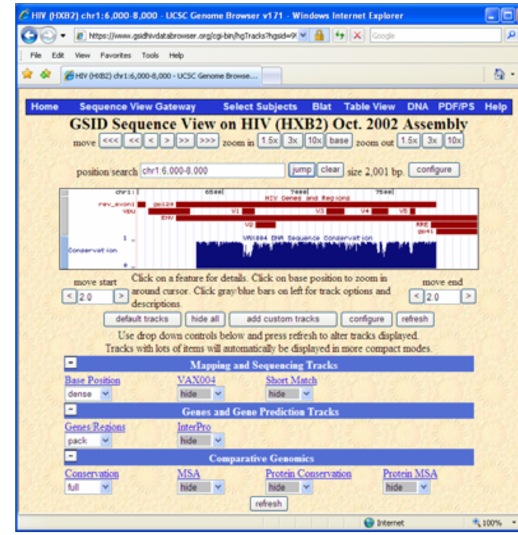

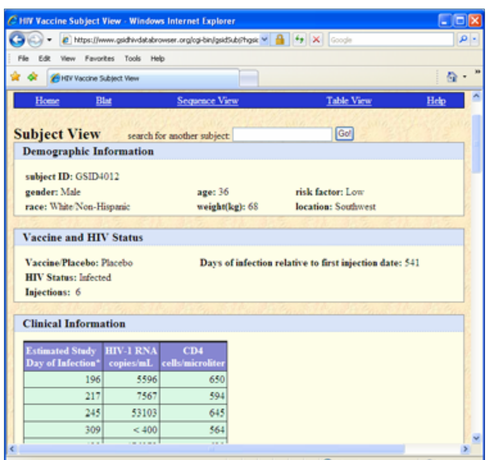

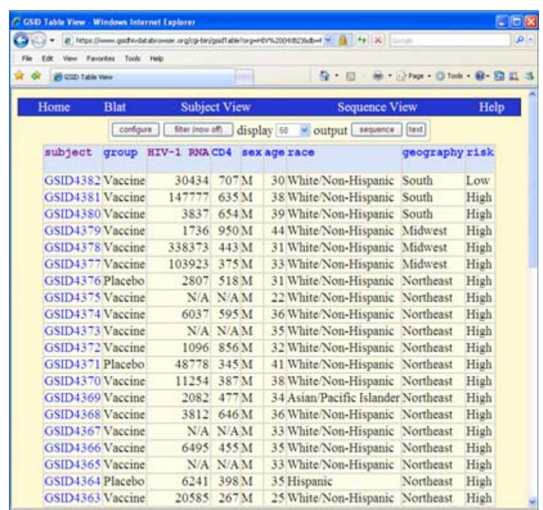

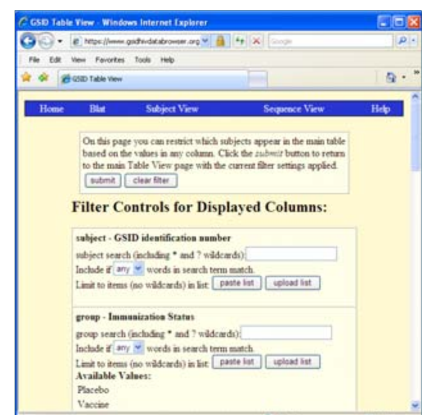

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GSID HIV Data Browser

- Relational database encompassing significant AIDSVAX clinical trial data
  - VAX004 data available 12/10/07 for beta testing
  - VAX003 data to be added in 2008
- Three primary views for accessing data
  - Subject View
  - Table View
  - Sequence View

GS ID GLOBAL SOLUTIONS FOR INFECTIOUS DISEASES

Subject View

Subject View

search for another subject: Go!

Demographic Information

subject ID: gsid4050

gender: Male | **age:** 43 | **risk factor:** High

race: White/Non-Hispanic | **weight(kg):** 86 | **location:** Northeast

Vaccine and HIV Status

Vaccine/Placebo: Vaccine

HIV Status: Infected

Injections: 7

Clinical Information

Days After Infection	HIV-1 RNA copies/mL	CD4 cells/microliter
114	827376	416
141	70180	501
182	43054	499
616	42759	359

Table View

Category	Description
Subject	GSID identification number
Group	Vaccine or placebo
Viral load	HIV-1 RNA in copies/mL
CD4	CD4 count in cells/μL
Sex	Gender at birth
Age	Age at enrollment
Weight	Weight in kilograms
Race	Self-reported race
Geography	Geographic region
Risk	Risk group

- Show data from all subjects in database
- Apply filters to select subjects
- View selected subjects in **Table View** and **Sequence View**

Table View

Home Blat Subject View Sequence View Help

configure | filter (now on) | display 50 | output | sequence | text

subject	group	HIV-1 RNA	CD4	sex	age	race	geography	risk
GSID4101	Vaccine	47892	219	F	29	Hispanic	South	High
GSID4141	Placebo	10765	548	F	36	Black/Non-Hispanic	Midwest	High
GSID4142	Vaccine	23649	621	F	29	Black/Non-Hispanic	Midwest	High
GSID4143	Placebo	73680	237	F	26	Black/Non-Hispanic	Midwest	High
GSID4144	Placebo	16977	173	F	29	Black/Non-Hispanic	Midwest	High
GSID4145	Placebo	7288	771	F	29	Black/Non-Hispanic	Midwest	High
GSID4244	Vaccine	4178	356	F	43	Other	South	High

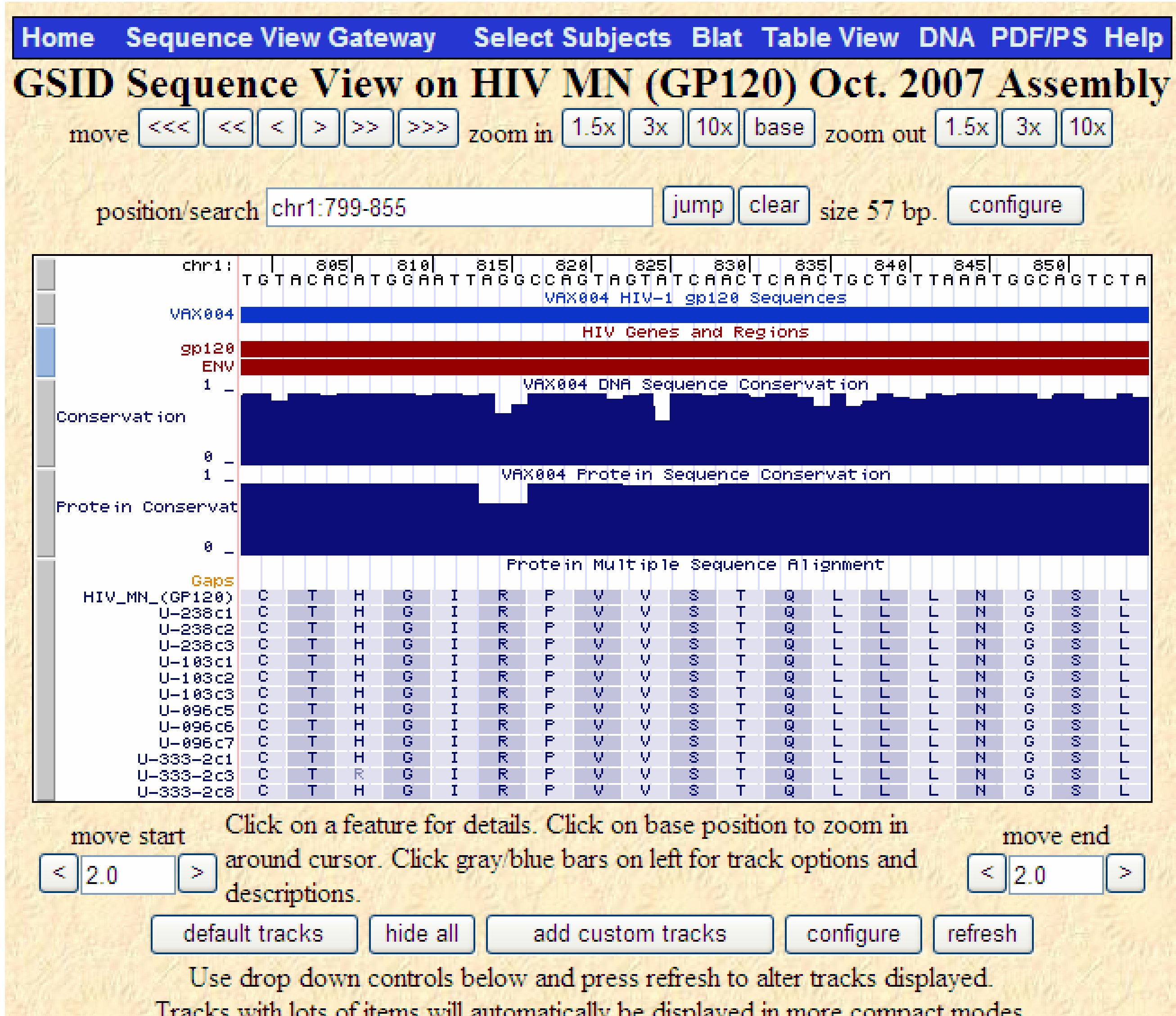
Displayed 7 out of 7 subjects passing filter.

Sequence View

- Rapid visual correlation of nucleotide and protein sequences from VAX004 viruses with multi-sequence alignment (MSA) tools
- DNA and protein conservation from MSA results

Sequence View

- VAX004 viral sequences from selected subjects, aligned with base genome (here, MN gp120)



Summary

- Established AIDSVAX clinical specimen repository at GSID
- Developed web-accessible AIDSVAX clinical and sequence database that is now ready for beta testing
- Completed preliminary sequence and phylogenetic analysis of early transmission viruses
- Generated preliminary data to define important antigenic regions within HIV-1 gp160
- Initiated efforts to identify and characterize broadly neutralizing antibodies

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