



Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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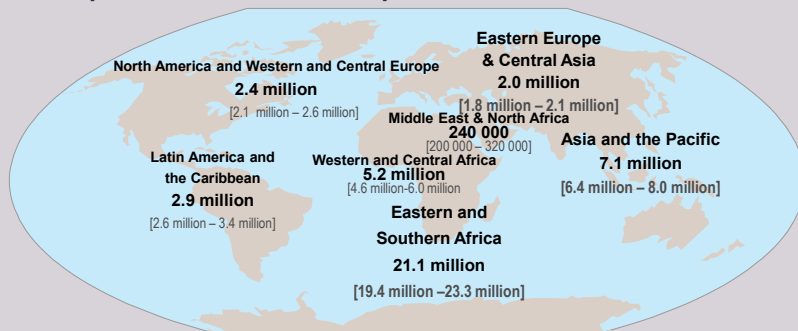


Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Estimated Numbers of Adults and Children with HIV 2025

HIV prevalence: 40.9 million persons with HIV

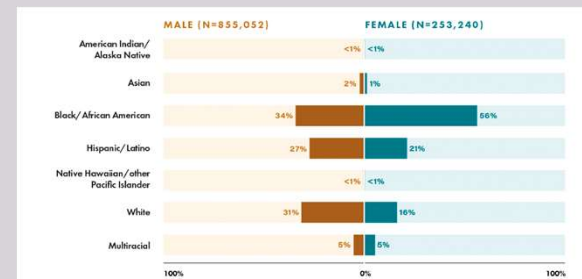


>75% access to antiretroviral therapy
HIV incidence: 1.2 million new infections/year

UNAIDS

Current US Epidemic

Prevalence: 1.1 Million



75% Male
70% Persons of Color

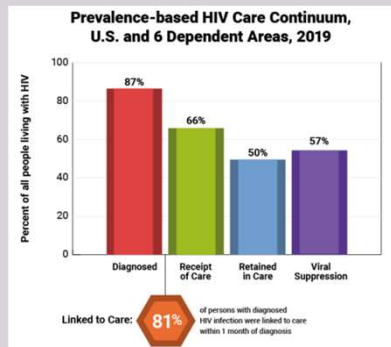
Diagnoses: 31,500 in 2023
CDC, 2024

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Gay, bisexual, and other men who have sex with men 68%
Heterosexual Contact 22%
IDU 10%

2030 US HIV Public Health Goals: Treatment Cascade

- 95 % Diagnosed
- 95% Undergoing Antiretroviral Therapy
- 95% Viral RNA Suppressed



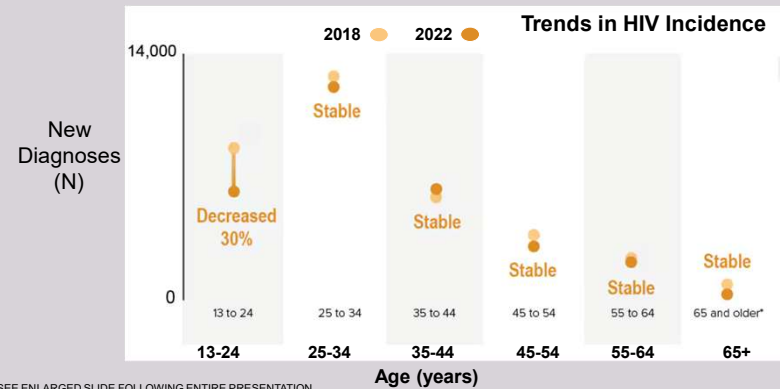
- >50% of Diagnoses are <35
- >50% Living with HIV are >50 years

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CDC

2030 US HIV Public Health Goals: Transmission

90% Reduction in Incidence by 2030

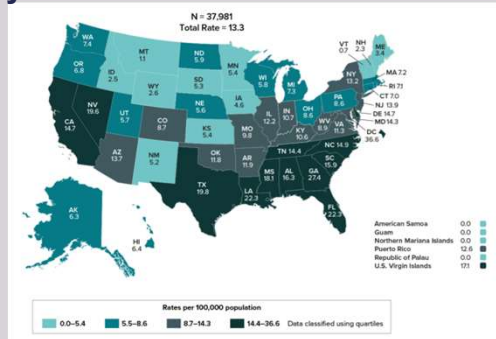


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CDC

Trends in the US Epidemic: Geography: Shift South and Out of Metro Areas

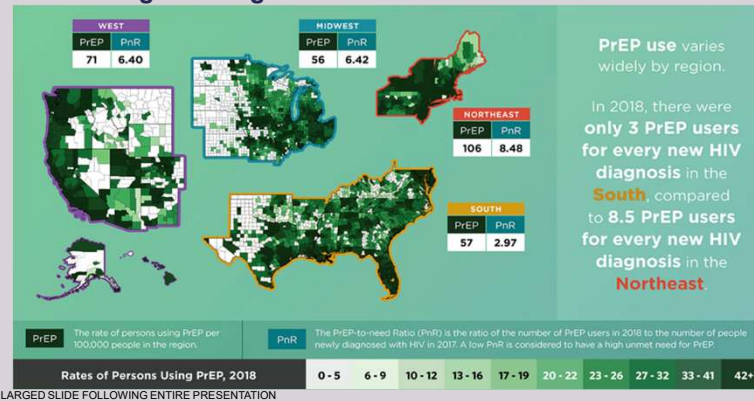
43% all new Diagnoses are in Southeast



Note. 2019 Data. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates <1,000 to reflect model uncertainty.
*Total estimate for the United States does not include data for Puerto Rico.

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PrEP-to-Need Ratio: PrEP using/HIV Diagnoses

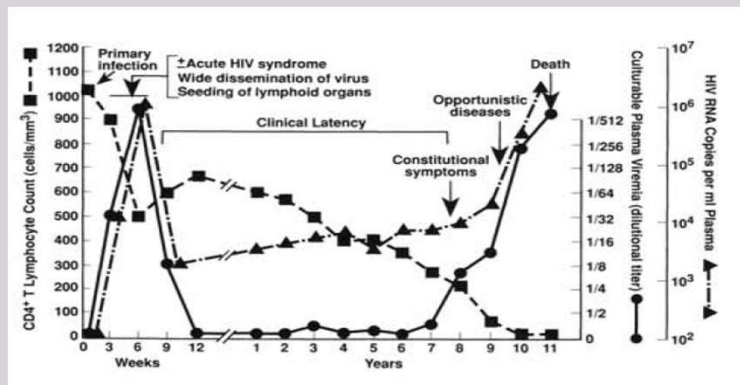


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32 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HIV Infection Course



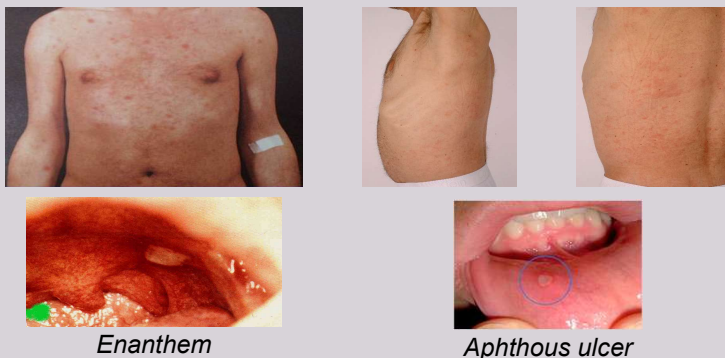
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Acute HIV Syndrome

Sign/Symptom	Percent Reporting		
	NEJM Review	Kenyan Sex Workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-27
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	2	nd	nd
Too ill to work	1	44	58

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Primary HIV-1 Infection Syndrome Maculopapular Trunk > Extremities



Question #1: HIV Presentation

- A 23-year-old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, diarrhea
- HIV-1/2 ELISA is reactive, viral RNA level 500,000 c/ml
- He is started immediately on antiretrovirals
- His supplemental assay is negative, and repeat assays sent 3 weeks, 3 months, and one year after starting antiretrovirals are also negative
- ELISA is reactive. HIV-2 assay is negative. Viral RNA on therapy is <40 c/ml.

Question #1: HIV Presentation

Which of the following is correct explanation for the absence of positive results with the supplementary HIV test?

- A. The patient was infected with a strain of HIV-1 that was not detected by the confirmatory assay
- B. The patient is HIV-infected but did not develop a positive results with the supplementary assay because of the early antiretroviral therapy intervention
- C. The patient never had HIV infection
- D. The patient had HIV but is now cured of HIV and antiretrovirals can safely be stopped

Early Antiretroviral Therapy

- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may remain negative
- HIV-1 DNA PCR has been useful in documenting infection

Question #2: HIV Presentation

- A 30-year-old individual who is completely adherent with long-acting cabotegravir as PrEP presents in January to your ED with low grade fever, fatigue, and mild myalgias
- 4th generation HIV testing is non-reactive, rapid Flu A testing is negative
- The ER physician asks whether this patient may have breakthrough HIV infection in the setting of PrEP, and whether further evaluation for HIV infection should be arranged

What would be your answer?

- A. The patient does not have breakthrough infections, because 4th generation assays are always reactive in the setting of breakthrough infection
- B. The patient does not have breakthrough infections, because breakthrough infections are always asymptomatic
- C. The patient may have breakthrough HIV infection, and further evaluation for HIV infection should be arranged
- D. The patient does not have breakthrough infections because breakthrough infections have never been reported with individuals completely adherent with long-acting cabotegravir

Long Acting Early Viral Inhibition (LEVI) Syndrome

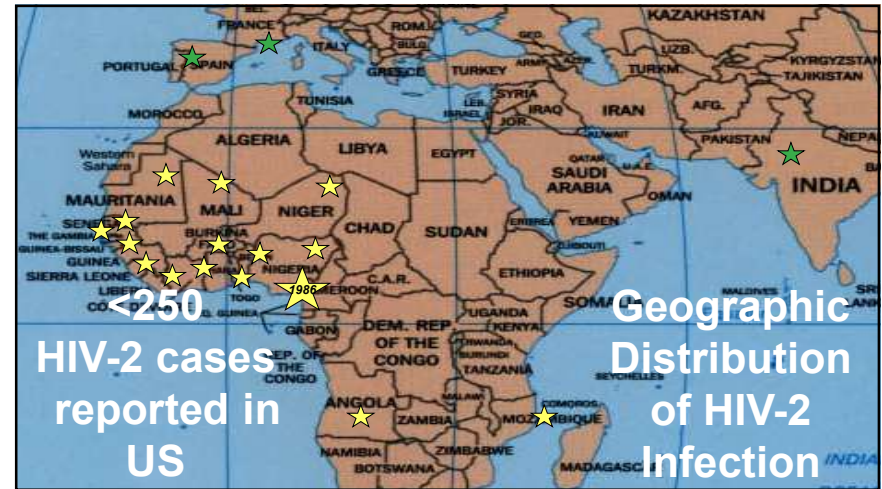
- True breakthrough infection
- Smoldering presentation- symptoms may be present
- Serologic testing: seroconversion, seroreversion, “serowaffling” may persist for months
- Drug resistance to integrase inhibitor can emerge

Question #3: HIV Presentation

- A 49-year-old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius positive for HIV-2 and negative for HIV-1
- CD4 cell count is 350 cells/ μ l

Which of the following is correct?

- HIV-2 is less pathogenic than HIV-1, and she only needs therapy with one antiretroviral drug
- She should not be treated with protease inhibitors because HIV-2 is naturally resistant to PIs
- She should not be treated with NNRTI therapy because HIV-2 is naturally resistant to NNRTIs
- Use of routine HIV-1 viral load assays is useful in-patient management



HIV-1 and HIV-2

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West/Central Africa	Worldwide
Local Distribution	Urban = Rural	Urban > Rural
Age-Specific Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average Age at Diagnosis	45-55	20-34
Maternal-Fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less Common (10X)	More Common
Therapy		
	NRTI, PI, INSTI, Corec	All Antiretrovirals
	NOT NNRTI, Fusion, (Capsid)	
Diagnosis		
Screening	HIV 1/2 ELISA	HIV 1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental (Qual HIV RNA)
Monitoring		
	HIV-2 RNA Assay	HIV-1 RNA Assay

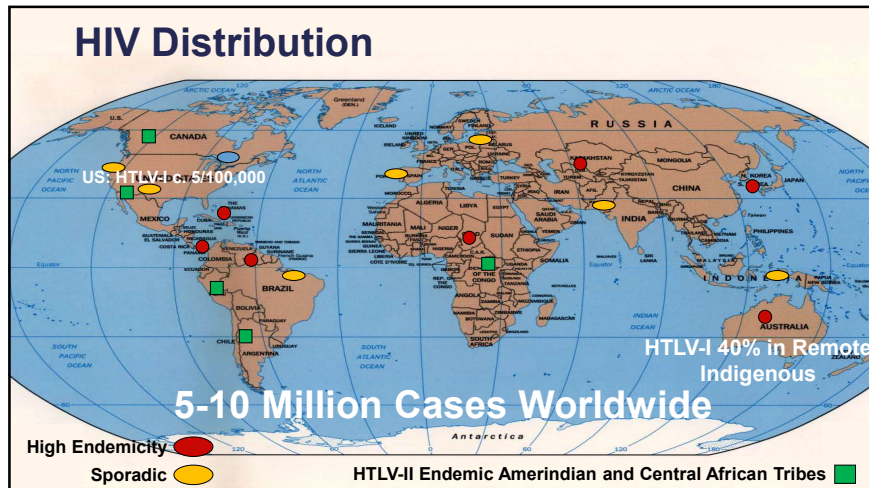
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Question #4

A 25-year-old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot.

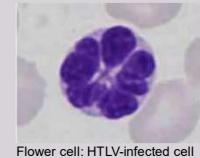
Which of the following statements is true?

- The risk of HTLV-I transmission can be entirely eliminated by caesarean section
- The risk of HTLV-I transmission will be entirely eliminated by not breastfeeding
- Breastfeeding will provide sufficient immunity to prevent infection with HTLV-I
- The risk of HTLV-I transmission will be significantly decreased but not entirely eliminated by avoiding breastfeeding
- There is no risk of HTLV-I disease. In this ethnic group, the HTLV-I test was likely a false positive



HTLV-I Transmission, Pathogenesis, Diagnostics

- Transmission
 - Breastfeeding
 - Prolonged duration: 20-30% seroconvert if breastfed >12 mos
 - High maternal HTLV proviral load in breastmilk:
 - 28.7 infections/1000 person months with 1.5% HTLV+ lymphs
 - Sexual
 - Transfusion
 - Risk of seroconversion: 40-60%
- Pathogenesis
 - Spread to CD4+ T cells
 - 1-4% of all CD4 cells become infected - multilobed nuclei "flower cells"
 - Spread is NOT continuous, but controlled shortly after infection takes place
 - Infection maintained in CD4 by persistence and clonal expansion
- Laboratory diagnosis by sequential testing ELISA/Western blot FDA approved
 - Can distinguish HTLV-I from HTLV-II



Question #5

- 37-year-old Jamaican female with diffuse pruritic rash (right), bone pain with lytic bone lesions
- WBC: 50,000, 90% lymphocytes

Which is most likely cause of her presentation?

- A. HTLV-I
- B. HTLV-II
- C. HIV-1
- D. HTLV-IV



HTLV-I Acute T Cell Leukemia (ATL)

Disease Onset

- Long Latency (>30 years)
- Small pediatric series in South America

Epidemiology

- Approximately 1% of HTLV- I infected adults
- M>F (Japan); M=F (Jamaica)

Associated syndromes

- Infectious
 - TB, MAC, Leprosy
 - PCP
 - Recurrent *Strongyloides*
 - Scabies esp. Norwegian scabies
- Noninfectious-hypercalcemia+lytic bone lesions

Therapy

- Cytotoxic chemotherapy
- AZT + Ifn
- Transplant
- Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
 - APPROVED in Japan for ATL
 - In US FDA approved for relapsed or refractory Sezary or mycosis fungoides
- Lenalidamide in trials

Question #6

- 38-year-old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence
- Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex
- WBC = 7500 cells/ μ l
- CD4 T cell = 1000 cells/ μ l
- CSF cell count: 10 cells/ mm^3 (lymphocytes)
- CSF protein: 75 mg/dl

Question #6

What other condition is the etiologic agent for this illness also associated with?

- A. Acute T cell leukemia
- B. Multiple sclerosis
- C. Variant Creutzfeldt-Jacob
- D. Hemorrhagic cystitis

HTLV-I Tropical Spastic Paraparesis /HTLV-1 Associated Myelopathy

- Epidemiology
 - <1% of HTLV-I develop HAM/TSP
 - The second most common neurologic syndrome in Jamaica after stroke
 - Latency may be short--several years
 - Female predominance

HTLV-I TSP/HAM

Presentation

- Spastic paraparesis
 - Lower > upper
 - Proximal > distal
- Bladder disturbance
- Hyperreflexia
- Positive Babinski reflex

Differential Diagnosis

- Cord compression
- B12 deficiency
- Syphilis
- HIV-1 myelopathy
- Multiple sclerosis

Therapy of HTLV-I TSP/HAM

- Corticosteroids
 - May slow progression and reduce disability
- Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
- Teriflunomide in trials (FDA- Approved for MS; pyrimidine synthesis inhib)
- Antiretroviral therapy is NOT effective

Question #7

- 62-year-old woman from Jamaica recently diagnosed with multiple sclerosis who is now experiencing her first relapse and has been prescribed a course of natalizumab
- She is also HTLV-1 seropositive; she has never had complications from HTLV, and you are consulted regarding treatment during therapy

Which of the following is most correct?

- A. She is at risk for HTLV disease progression and should not be treated with natalizumab
- B. She is not at risk for HTLV disease progression and can be treated with natalizumab
- C. She may be treated with natalizumab but should also be treated with antiretroviral therapy to prevent HTLV reactivation
- D. The HTLV serologic test may be false positive in multiple sclerosis, and she should first be tested for HTLV DNA, if she is DNA positive, she should not be treated with natalizumab

Question #8

- A 42-year-old man from the Haiti presents with fever, moderate respiratory distress, and nonproductive cough
- HIV-1/2 ELISA is reactive, and discriminatory test is positive for HIV-1
- A PCR test of the induced sputum is positive for *Pneumocystis jirovecii*
- On evaluation the lymphocyte count is 2,000 cells/ μ l; the CD4 count is 750 cells/ μ l and the hematology technician remarks that some of the lymphocytes are "flower cells"

Which of the following is most correct in explaining these findings?

- A. The patient has HIV and B cell lymphoma
- B. The patient has HIV infection, and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis pneumonia*
- C. The patient has HTLV-1 infection only the HIV test is a false positive
- D. The patient has both HIV infection and HTLV-1 infection

Pearls

HTLV-1 Infection

- Asymptomatic - 95%
- Acute T cell Leukemia
- HAM/TSP
- But also
 - Bronchiectasis
 - Uveitis
 - Rheumatologic syndromes
 - Lymphocytic pneumonitis
 - Infective Dermatitis (pediatric)
- "Flower" cells
 - Lymphocytes with HTLV provirus present
 - Frequency in HIGHER in ATL and HAM/TSP
 - NOT an indication for specific therapy
- NOT a contraindication for transplantation
- No indication for ART

Associated Infections

- *Strongyloides* hyperinfection
- Norwegian Scabies
- *Pneumocystis*
- MAC

HTLV-II

- Not a cause of disease
- A distractor

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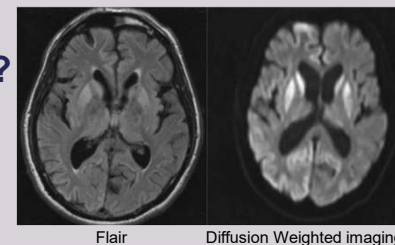
Slow Viruses

Question #9: Prion Diseases

68-year-old butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG

How was this illness most likely acquired?

- A. Contact with elk brains
- B. Contact with sheep brains
- C. Contact with pork brains
- D. A spontaneous event



Prion Diseases: Transmissible Spongiform Encephalopathies

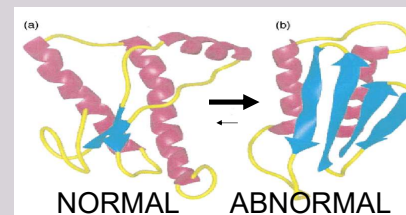
- **Spontaneous (N=~6000 worldwide PER YEAR)**
 - Sporadic Creutzfeldt-Jakob disease (sCJD)
- **Hereditary (N ~600-900 PER YEAR worldwide)**
 - Autosomal Dominant
 - Familial (fCJD)
 - Gerstmann-Straussler-Sheinker (GSS)
 - Fatal Familial Insomnia (FFI)
 - Fatal Sporadic Insomnia (FSI)
- **Associated with specific exposure**
 - Ingestion of beef from cows with Bovine Spongiform Encephalopathy
 - Denoted "Variant CJD", "vCJD" (N = 228 TOTAL cases, most recent case 2024)
 - Blood transfusion from individual with vCJD (4 cases)
 - Human brains
 - Kuru (N= ~2700 TOTAL cases; last known case reported 2009)
- **Associated with a medical procedure (N ~ 450 TOTAL cases)**
 - Iatrogenic "iCJD"

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<https://www.ucl.ac.uk/brain-sciences/prion/about-us/kuru>

Prion Disease Pathogenesis A. Initiation

The prion protein is a host protein with a normal and abnormal conformation



Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

Prion Disease Pathogenesis

B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation

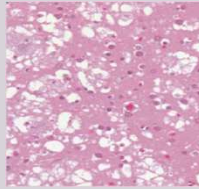


Prion Protein
Mutant Conformation

Direct contact



Prion Protein
Mutant Conformation



Disaggregase chaperone proteins
may scavenge these proteins
with mutant conformation

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Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- MOST common human Transmissible Spongiform Encephalopathy (TSE)
 - 95% cases
- Incidence estimated 1 per million
 - US: 0.1/million in <55 yo, 5.3/million >55 yo
 - Mean age of onset is 60 years

Dementia Comparison

Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2 y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4 y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α -Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate, Pons Thalamus Ovoid Nuc

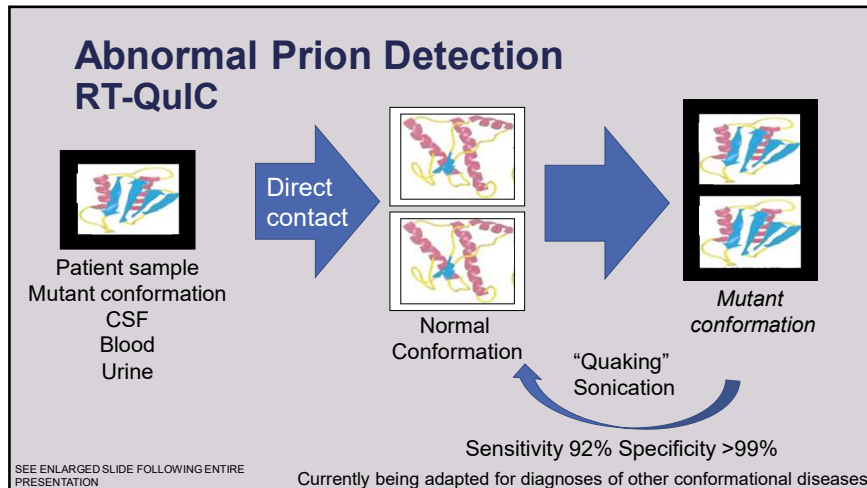
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Question #10: Prion Diseases

- A 68-year-old man with dementia progressing over the last 6 months undergoes evaluation

Which of the following CSF results is most consistent with Creutzfeldt-Jakob Disease?

- 14-3-3 protein: Positive
- RT-QuIC: Positive
- T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
- A β 42: 1250 pg/mL (normal >1026 pg/mL)



Spontaneous Creutzfeldt-Jacob Disease (sCJD) Typical Clinical Presentation

- Classic Clinical Triad
 - Dementia
 - Myoclonus
 - EEG: periodic sharp waves
- Rapid progression
- RT-QuIC elevated
- Supportive, not specific:
 - Elevated Tau
 - 14-3-3

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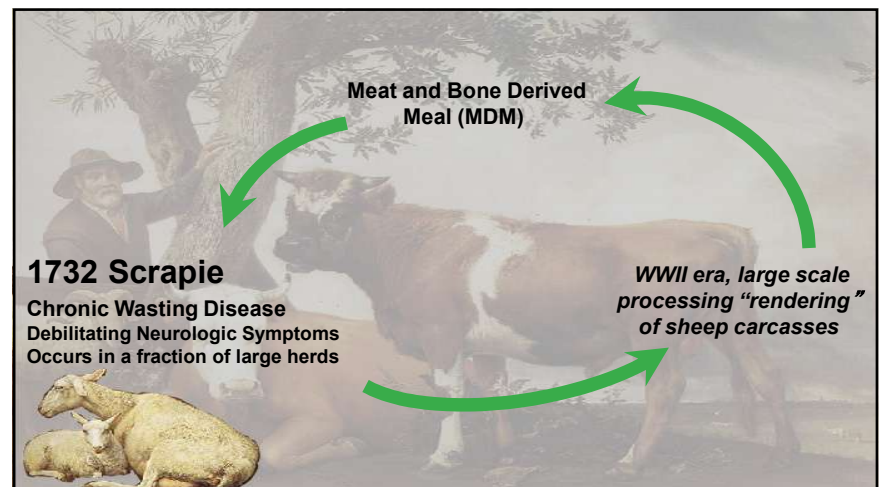
Herran, BMC Neurology 2018

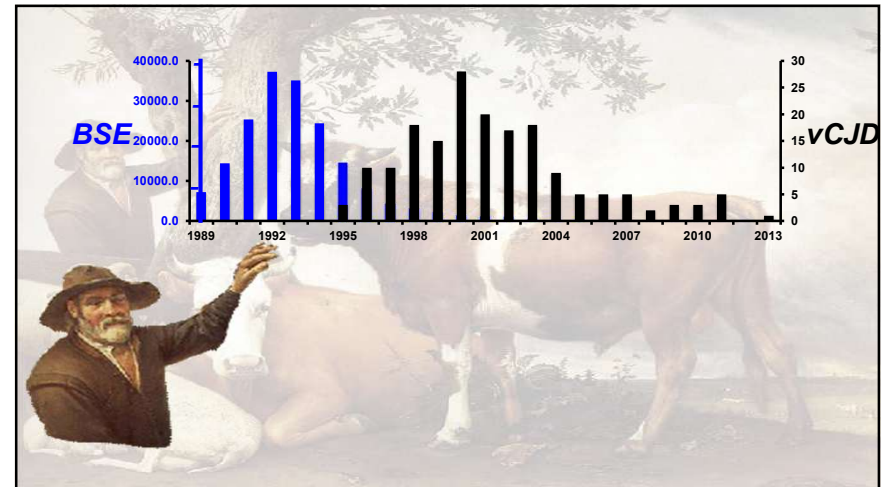
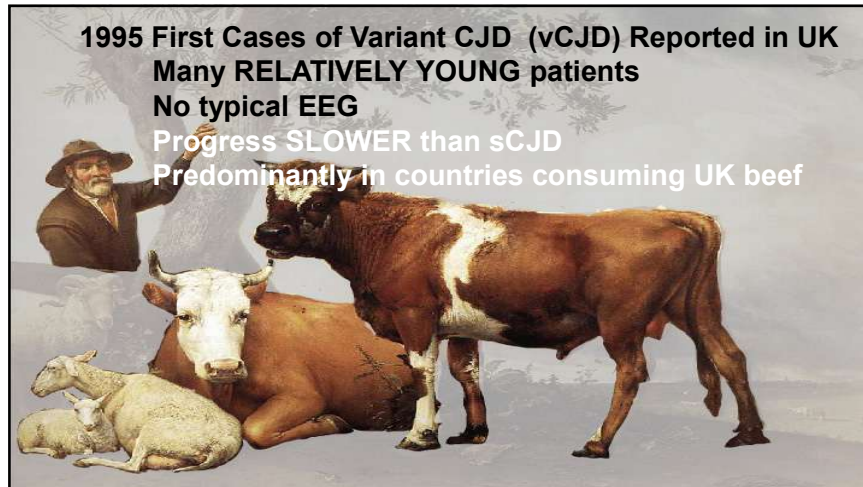
Question #11: Prion Diseases

- A 44-year-old man presents with dementia progressing over the last 18 months
- He was born in rural Indonesia, lived in London and ate beef from 1985-2025, then moved to Philadelphia

Which of the following diseases is most likely the cause of his symptoms?

- Kuru
- Variant Creutzfeldt-Jacob Disease
- Familial Creutzfeldt-Jacob Disease
- Rabies

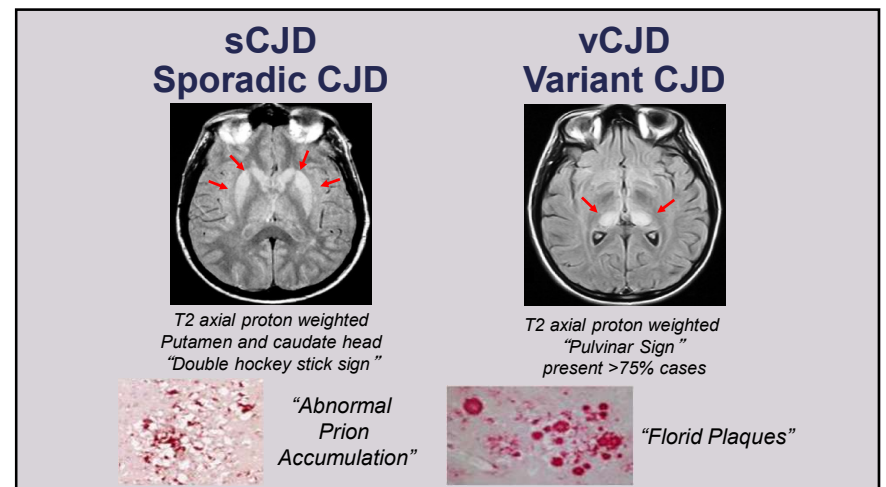




Numbers of vCJD Cases Worldwide

United Kingdom	177
France	26
Spain	5
US	4
All acquired OUTSIDE of US	
Ireland	4
Netherlands, Italy	3
Portugal, Canada, Italy	2 each
Saudi Arabia, Japan, Taiwan	1 each
Single cases reported 2018, 2021	

(<https://www.ecdc.europa.eu/en/vcjd/> 2024)



Question #12: Prion Diseases

- A 40-year-old man recently emigrated from Japan presents with rapidly progressing dementia over the course of months
- He underwent a meningioma resection with dura mater graft in Japan 35 years ago
- He is an avid deer hunter and consumes venison

What is the most likely cause of his dementia?

- A. Iatrogenic CJD from the dura mater graft
- B. CJD from eating deer
- C. HTLV-I
- D. Alzheimer's disease

Iatrogenic CJD ~450 cases

Definite Causes

- Pituitary extracts
 - Human Growth Hormone
 - Delay may be >40 y
- Dura mater grafts
 - Mostly Lyodura brand
 - Japan has highest number of cases
- Transplants (RARE)
 - Corneal
 - Pericardium
 - Liver
- Instrumentation/Laboratory Accident
 - Implanted EEG
 - Stereotactic procedures

No Link

- Vaccines
- Feces
- Saliva
- Sputum
- Bovine insulin
- Semen, vaginal secretions

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Summary

	sCJD	Familial CJD	iCJD	vCJD
Source	Spontaneous event	Autosomal Dominant	Human growth hormone Dura mater graft	Ingested beef
Distribution	Worldwide	Worldwide	Human growth hormone: US, Europe Dura mater graft: Japan	Linked to Beef originating largely in UK. US cases all have travel history
Median Age of onset (y)	68	40-60	51-58	26-28
Approximate Survival	8 months	up to 5 y	15 months	14 months
EEG	Periodic sharp waves	Variable	few data	No Periodic Sharp Waves
MRI (DWI)	"Double Hockey Stick"	Variable	Few Data, Double Hockey Stick	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	Abnormal Prion Protein deposits	Abnormal Prion Protein deposits	"Florid Plaques"

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Prions Reference Material

CJD and Recommendations

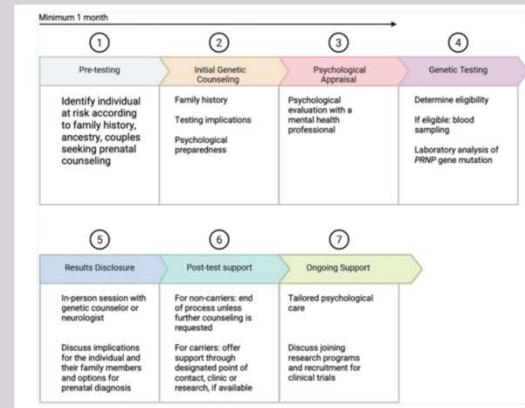
Patient

- Detailed history
- Blood/urine testing for presence of prions RT-QuIC
- Referrals
- Resources

Family Members

- Detailed history/Detailed discussion
- No role for RT-QuIC routine screening for presence of prions in blood or urine
- Genetic testing for prion variants may be useful
- Referrals
- Resources

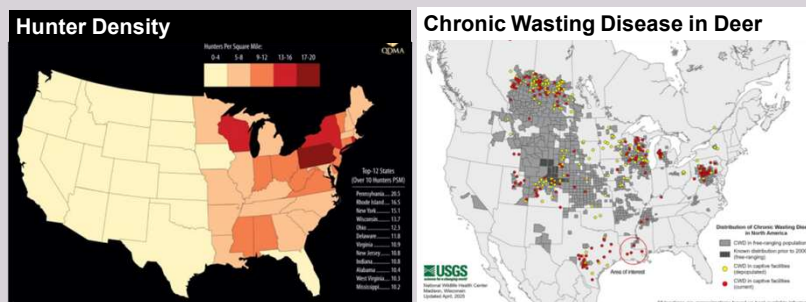
CJD and Recommendations



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Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

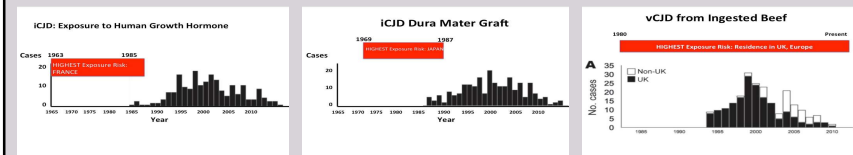
Geography (rural) or activity (hunting) are DISTRACTORS



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Transmissible Spongiform Encephalopathy: Time and Place

Mode of Transmission	Geographic Region	Risk Window
Beef Ingestion	UK, France, Europe	1980 – Present
Human Growth Hormone	France	1963 – 1985
Dura Mater Graft	Japan	1969 – 1987



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Kuru “Shivering, Trembling”

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
 - Ambulant, leaning (pictured)
 - Sedentary
 - Terminal “laughing death”
 - “Florid plaques” (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991
- Last recorded case 2009



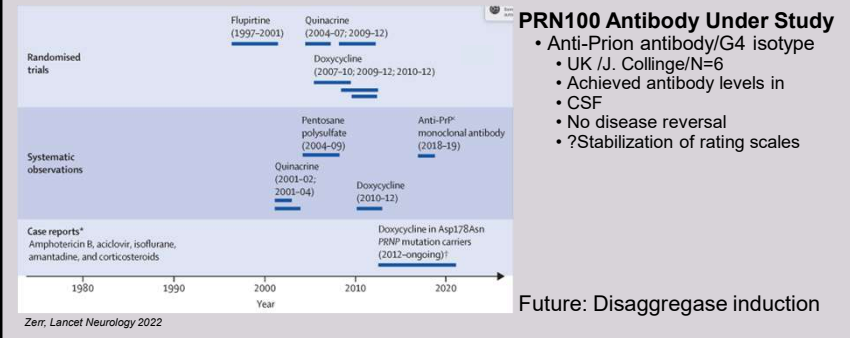
CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferral
 - Dura mater graft or human growth hormone
 - Donors with CJD or family history of CJD
 - Residence in Europe after 1980
 - Transfusion in Europe after 1980
 - Bovine insulin after 1980 unless certain that insulin was not from UK

Transmissible Spongiform Encephalopathy Infection Control Issues

- **Universal precautions**
- **No confirmed occupational transmissions**
 - CJD in health care workers occurs, occupational links have been suggested
- **Incinerate single use instruments**
- **Inactivate other instruments and materials**
 - 1N NaOH
 - autoclave 121o C, 15 psi 30 min
 - Formic acid for tissue sections
 - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
 - REMEMBER: Infectivity is STABILIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
 - <http://www.who.int/csr/resources/publications/bse/whocdscsrph2003.pdf?ua=1>

Transmissible Spongiform Encephalopathy Multiple Trials BUT NO FDA Approved Therapy



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Resources

- **RT-QuIC: Case Western**
 - <https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information>
- **Diagnostic Criteria**
 - <https://case.edu/medicine/pathology/research/national-prion-disease-pathology-surveillance-center/human-prion-diseases/diagnostic-criteria-creutzfeldt-jakob-disease-cjd>
- **Epidemiology**
 - <https://www.cdc.gov/prions/cjd/resources.html>
- **Patient Support**
 - <https://cjd.foundation.org/other-resources>
- **fmdarelli3@gmail.com**