

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

**IDBR**  
**INFECTIOUS DISEASE BOARD REVIEW**  
**AUGUST 20-24**  
**2022**

**Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**

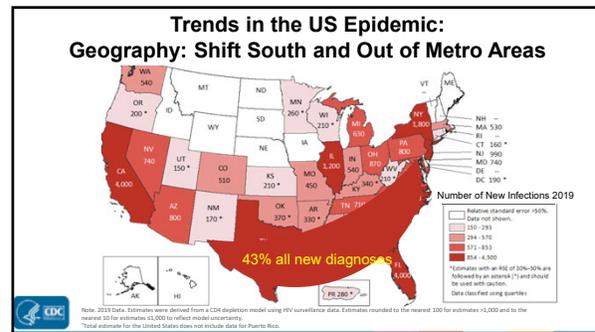
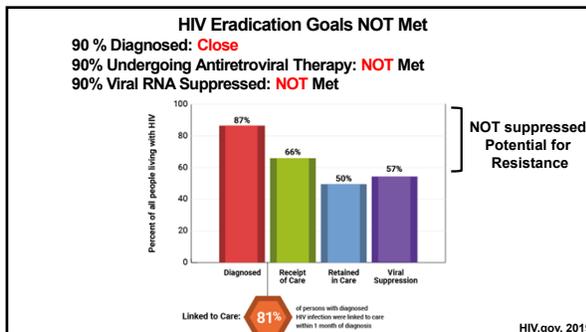
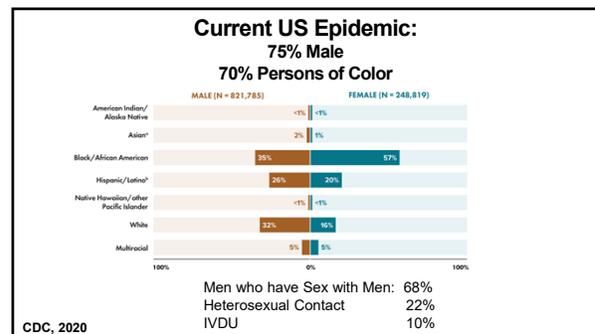
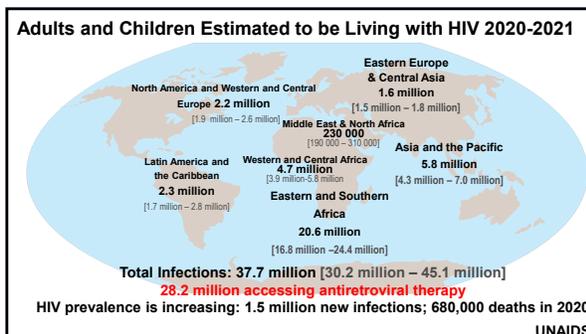
Frank Maldarelli, MD, PhD\*  
Bethesda, Maryland

6/24/2022

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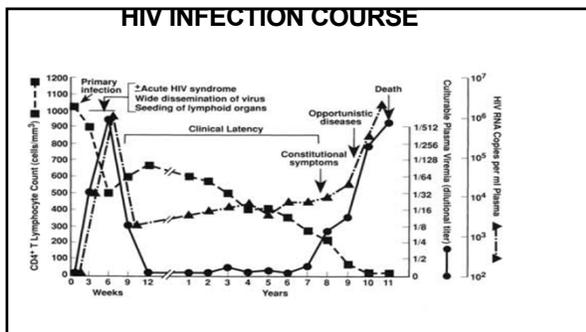
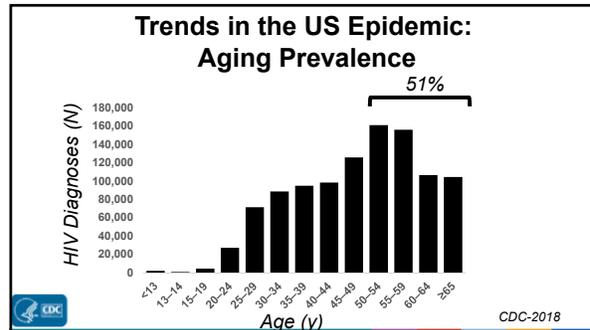
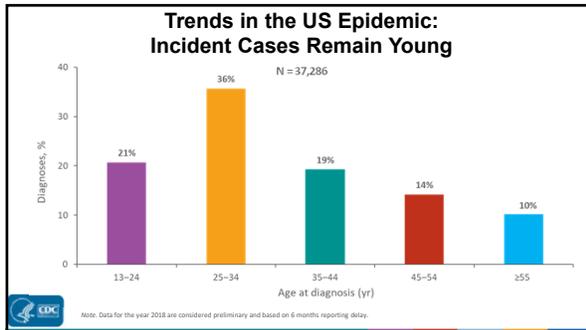
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- None



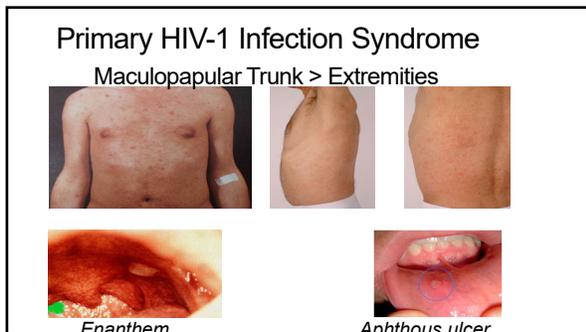
# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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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	nd	44	58



### HIV Diagnosis: Question #1

A 23 year old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, adenopathy. 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 remains reactive. HIV-2 assay is negative.

Viral RNA on therapy is <40 c/ml.

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## HIV Diagnosis: Question #1 continued

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

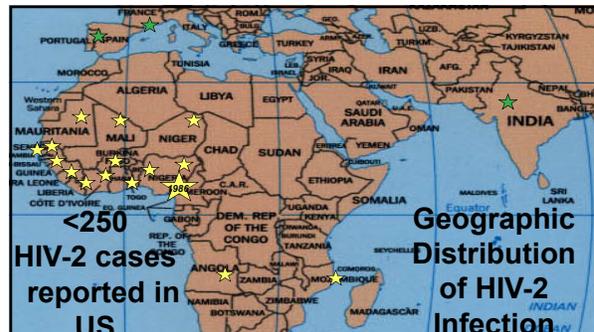
- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may remain negative
- HIV-1 DNA PCR has been useful in documenting infection

## HIV Clinical Presentation: Question #2

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/ $\mu$ l.

Which of the following is correct?

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



## HIV-1 and HIV-2

Characteristic	HIV-2	HIV-1
<b>Epidemiology</b>		
Geography	West /Central Africa	Worldwide
Local Distribution	Urban>rural	Urban>rural
Prevalence	Stable or Decreasing	Increasing
<b>Pathogenesis</b>		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without RX)	0-4%	20-35%
Kaposi Sarcoma	Less common (10X)	More common
<b>Therapy</b>	NRTI, PI, INSTI, Corec	NRTI, PI, NNRTI
	<b>NOT</b> NNRTI <b>NOT</b> Fusion	INSTI, Corec, Fusion
<b>Diagnosis</b>		
Screening	HIV1/2 ELISA	HIV1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental
		Qual. HIV RNA)
<b>Monitoring</b>	HIV-2 RNA Assay	HIV-1 RNA assay

## Question #3

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 jiroveci*. On evaluation the lymphocyte count is 2,000 cells/ $\mu$ l; the CD4 count is 750 cells/ $\mu$ 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

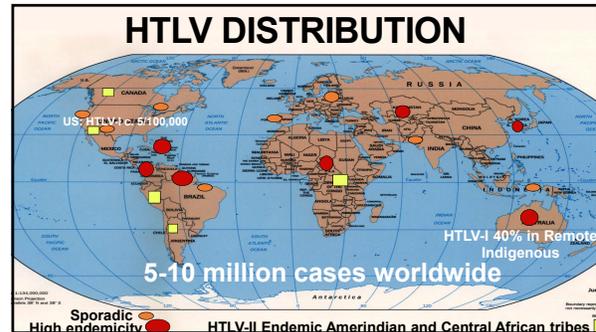
# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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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?

- HTLV-I
- HTLV-II
- HIV-1
- 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/ $\mu$ l

CD4 T cell = 1000 cells/ $\mu$ l

CSF cell count: 10 cells/ $\text{mm}^3$  (lymphocytes)

CSF protein: 75 mg/dl

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## Question #6 Continued

The etiologic agent associated with this illness is 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  | •Differential Diagnosis |
| ▪Spastic paraparesis <ul style="list-style-type: none"><li>○Lower&gt;upper</li><li>○Proximal&gt;distal</li></ul> | ▪Cord compression       |
| ▪Bladder disturbance   | ▪B12 deficiency         |
| ▪Hyperreflexia   | ▪Syphilis               |
| ▪Positive Babinski reflex  | ▪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 man from Jamaica with rheumatoid arthritis has not responded to several antirheumatic drugs including the methotrexate that he is currently taking. He is now being considered for treatment with rituximab. He is hepatitis B positive (surface antibody positive, surface antigen negative) and HTLV-1 positive (antibody and PCR). He will continue to receive Tenofovir + FTC to prevent HBV reactivation, and you are consulted regarding the development of HTLV-I drug resistance. Which of the following is most correct:

- A. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an additional reverse transcriptase inhibitor like doravirine.
- B. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an integrase inhibitor like dolutegravir
- C. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should also receive a protease inhibitor like darunavir.
- D. He is not at risk for the development of HTLV-I drug resistance.

## Question #7

62 year old man from Jamaica with rheumatoid arthritis has not responded to several antirheumatic drugs including the methotrexate that he is currently taking. He is now being considered for treatment with rituximab. He is hepatitis B positive (surface antibody positive, surface antigen negative) and HTLV-I positive (antibody and PCR), but has never had complications from HTLV. He will continue to receive Tenofovir + FTC to prevent HBV reactivation, and you are consulted regarding the use of antiretrovirals in HTLV in this circumstance. HTLV-I drug resistance. Which of the following is most correct:

- A. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an additional reverse transcriptase inhibitor like doravirine.
- B. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should receive an integrase inhibitor like dolutegravir
- C. He is at risk for the development of HTLV-I drug resistance with this two drug combination. He should also receive a protease inhibitor like darunavir.
- D. He is not at risk for the development of HTLV-I drug resistance.

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## Question #8

A 56 year-old HTLV-I infected woman is diagnosed with multiple myeloma. She has never had complications from HTLV-I infection and is otherwise eligible for autologous bone marrow transplant. You are consulted regarding her eligibility for chemotherapy vs. chemotherapy and autologous bone marrow transplant. Which of the following is most correct:

- A. She should not undergo autologous BMT because of reduced overall survival from ATL or other secondary malignancy in the post transplant period
- B. She should not undergo autologous BMT because of the high risk of graft failure
- C. She can undergo autologous BMT, but she should be treated with antiretroviral therapy from induction, until she recovers her counts (WBC>500 cells/ $\mu$ l)
- D. She can undergo autologous BMT; her 3 year survival is equivalent to individuals without HTLV-I 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 is HIGHER in ATL and HAM/TSP
  - NOT an indication for specific therapy

### Associated Infections

- Strongyloides hyperinfection
- Norwegian Scabies
- Pneumocystis
- MAC

### HTLV-II

Not a cause of disease  
A distractor

Thanks to Tamara Nawar, Ying Taur, Anna Kaltsas (SKMC, NYC)

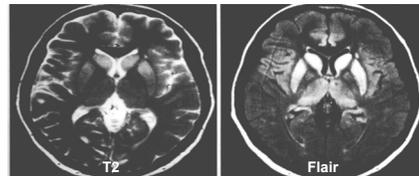
## SLOW VIRUSES

## Prion Disease Question #1

68 y. o. butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

Acquisition of this illness was most likely due to:

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



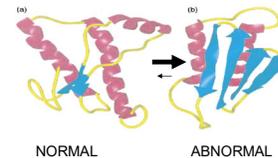
## Prion Diseases: Transmissible Spongiform Encephalopathies

- Spontaneous (N=6000 worldwide per year)
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
- Associated with specific ingestion
  - Beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "vCJD" (N ~ 220 total cases)
  - Human brains
    - Kuru (N= ~2700 total cases)
- Associated with a medical procedure (N ~ 450 total cases)
  - Iatrogenic
  - Denoted "iCJD"
- Hereditary (N ~ 600-900 worldwide per year)
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)

## Prion Disease Pathogenesis

### A. Initiation

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

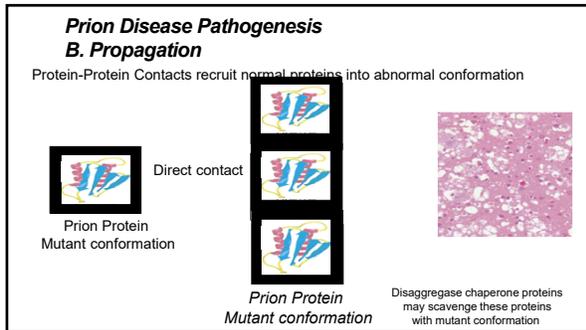


Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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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

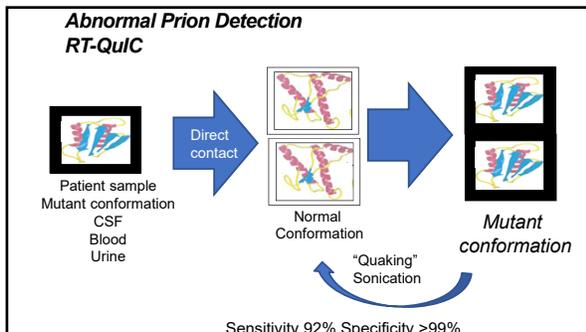
### Dementia Comparison

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	$\alpha$ -Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate, Pons Thalamus Ovoid Nac

### Prion Disease Question #2

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 $\beta$ 42: 1250 pg/mL (normal >1026 pg/mL)



### Spontaneous Creutzfeldt-Jacob Disease

#### Typical Clinical Presentation

- Rapid progression
- RT-QuIC elevated abnormal prion protein
- 14-3-3 not specific for CJD
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves

Herron. BMC Neurology 2018

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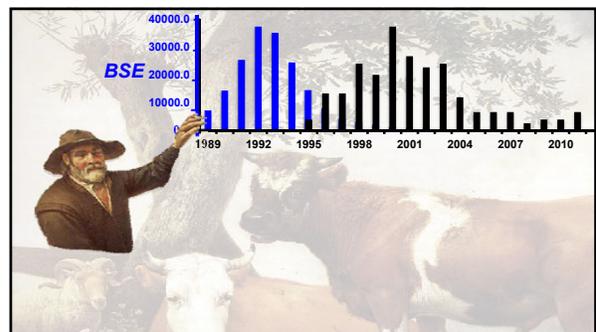
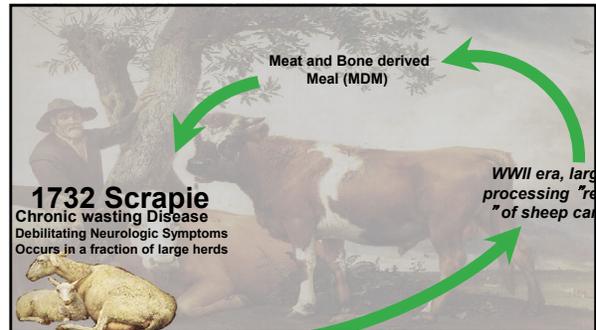
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## Prion Disease Question #2

A 40 year old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1985 – 2010, then moved to Philadelphia.

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

- A. Kuru
- B. variant Creutzfeldt-Jacob Disease
- C. Familial Creutzfeldt-Jacob Disease
- D. Rabies



## Question #4 vCJD Geographic Distribution

Residence in which of the following countries after 1980 represents the highest risk for acquiring variant CJD (vCJD):

- A. France
- B. Borneo
- C. United States
- D. Australia
- E. Argentina

## Numbers of vCJD Cases Worldwide

- United Kingdom: 178
- France: 28
- Spain: 5
- US: 4  
  - (ALL infections acquired OUTSIDE of US)
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

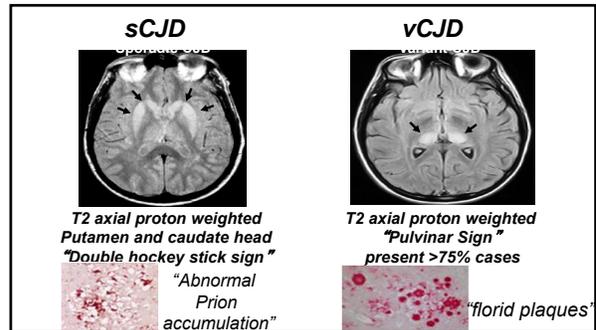
(Nat'l CJD Res. Surv. Unit, U. Edinburgh, www.cjd.ed.ac.uk 2019)

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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**vCJD vs. sCJD**

	sCJD	vCJD
Source	Spontaneous event	Ingested beef
Distribution	Worldwide	Linked to Beef originating largely in UK
Median Age (y)	68	28
Progression	SHORTER	LONGER
EEG	Typically abnormal	NOT Typically abnormal
MRI Basal ganglia	"Double Hockey Stick"	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	"Florid Plaques"



**Prion Diseases Question #5**

A 49 year old man recently emigrated from Japan presents with rapidly progressing dementia.

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:

- iatrogenic CJD from the dura mater graft
- CJD from eating deer.
- HTLV-I
- Spontaneous CJD

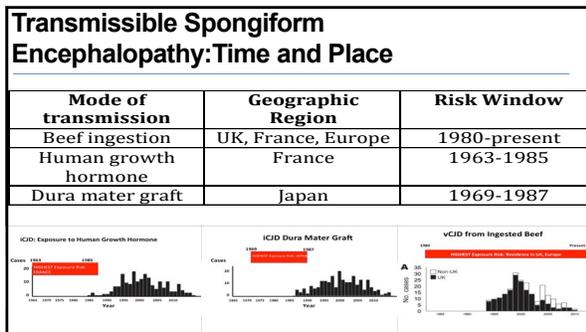
**iatrogenic CJD ~450 cases**

**Definite Causes**

- Pituitary extracts
  - Human Growth Hormone
  - Delay may be >30 y
  - (Role in AD as well?)
- Dura mater grafts
  - Mostly Lyodura brand
- Transplants
  - Corneal
  - Pericardium
  - Liver
- Instrumentation/Laboratory accident
  - Neurosurgeons/implantable Neurosurgical-implanted EEG, stereotactic procedures
- Pathologist
- Scientists (Emilie Jaumain, FR)

**No Link**

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



**Zoonotic Transmission CJD**

**Documented Risk**

- Ingestion of Beef
  - Geographically limited
  - Emphasis on UK, France

**No Documented Risk**

- Mink:
  - Transmissible Mink Encephalopathy
- Elk, Mule deer:
  - Chronic Wasting Disease
- Sheep, goats
  - Scrapie
- Cat:
  - Feline Spongiform Encephalopathy

# 34 – Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

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## CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferred from blood donation
  - 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

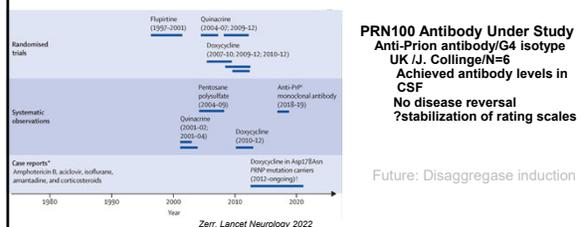
## CJD and Recommendations

- **Patient**
  - Detailed history
  - Blood/urine testing for presence of prions
  - Referrals
  - Resources
- **Family members**
  - Detailed history/Detailed discussion
  - No role for routine screening for presence of prions in blood or urine
  - Genetic testing for prion variants may be useful
  - Referrals
  - Resources

## 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 121° 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 NO FDA Approved Therapy



## 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



## Resources

- **RT-QuIC: Case Western**
  - <https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information>
- **Epidemiology**
  - <https://www.cdc.gov/prions/cjd/resources.html>
- **Patient support**
  - <https://cjd.foundation.org/other-resources>
- faldarelli3@gmail.com