

Opportunistic infections (OIs) in HIV Patients

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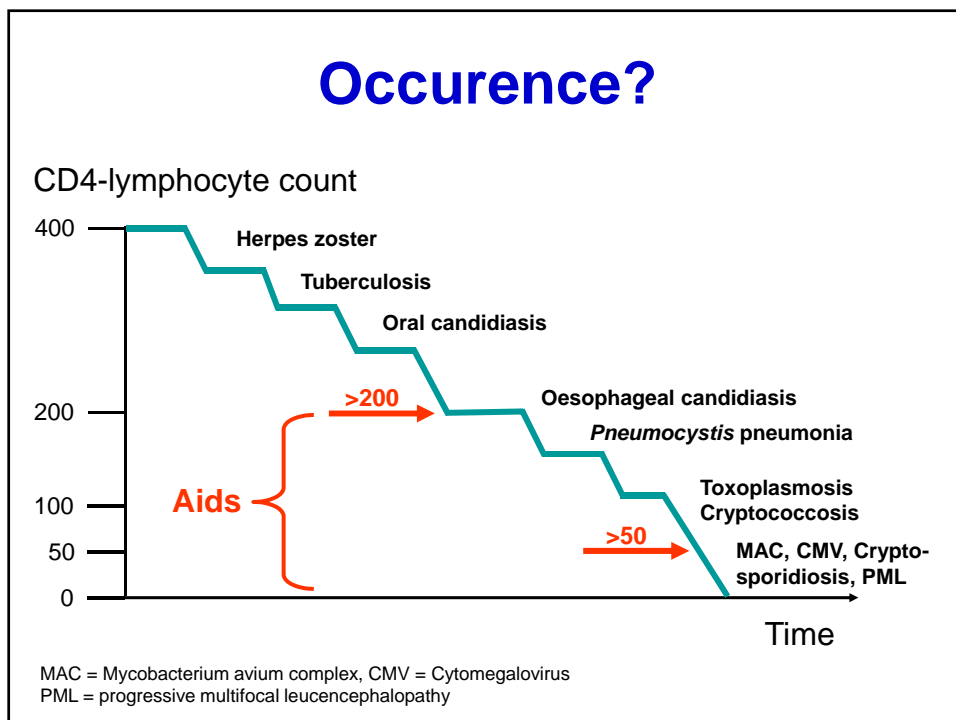
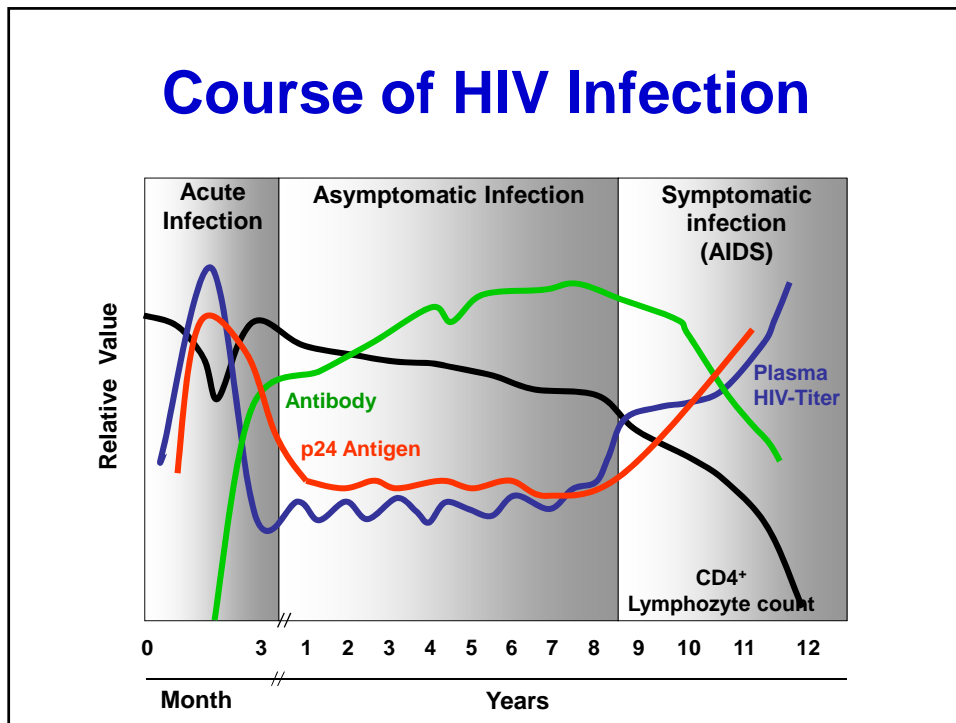
Outline

- Clinical cases and differential diagnoses and diagnostic approach
- Literature review

Treating Opportunistic Infections among HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America

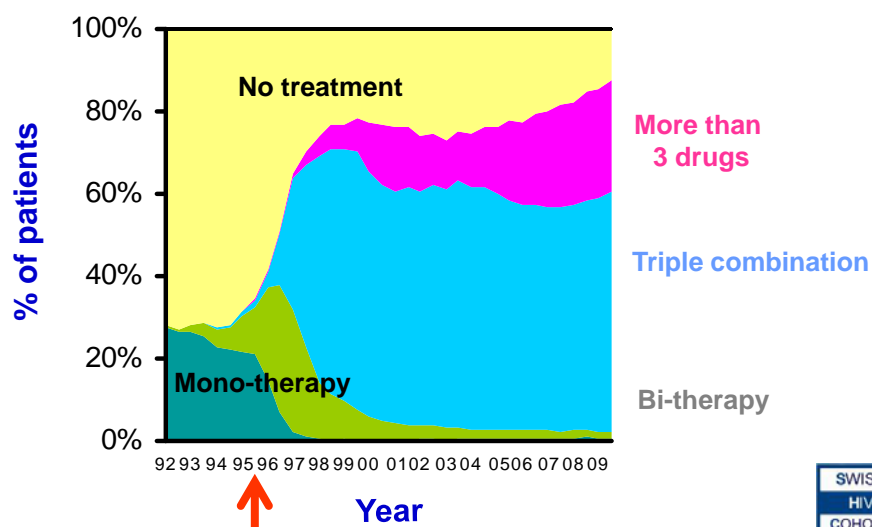
Clinical Infectious Diseases 2005;40:S131-235

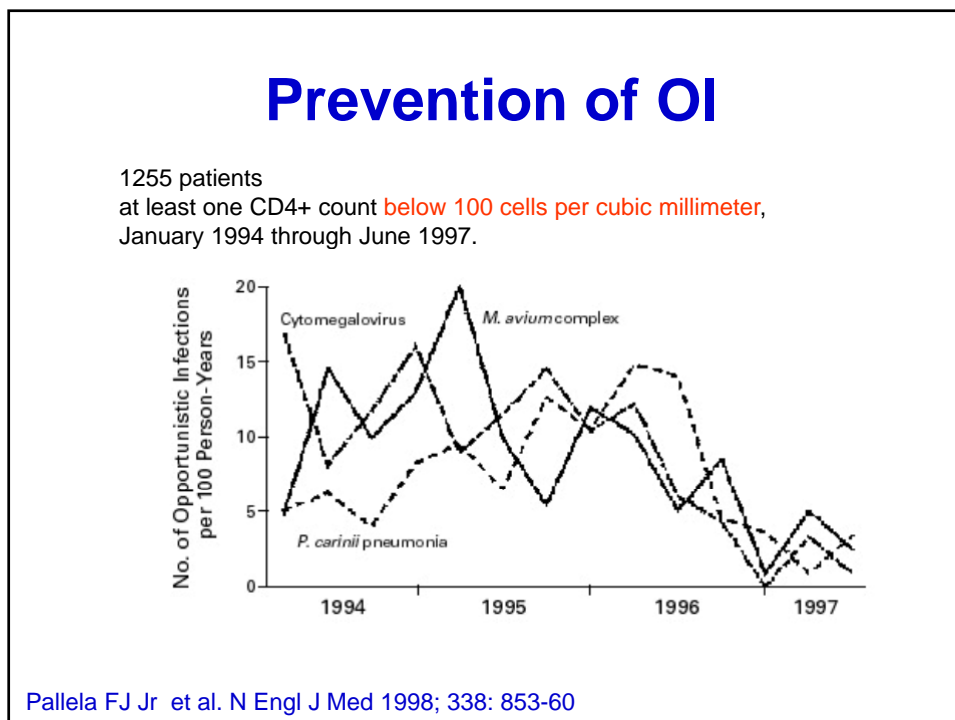
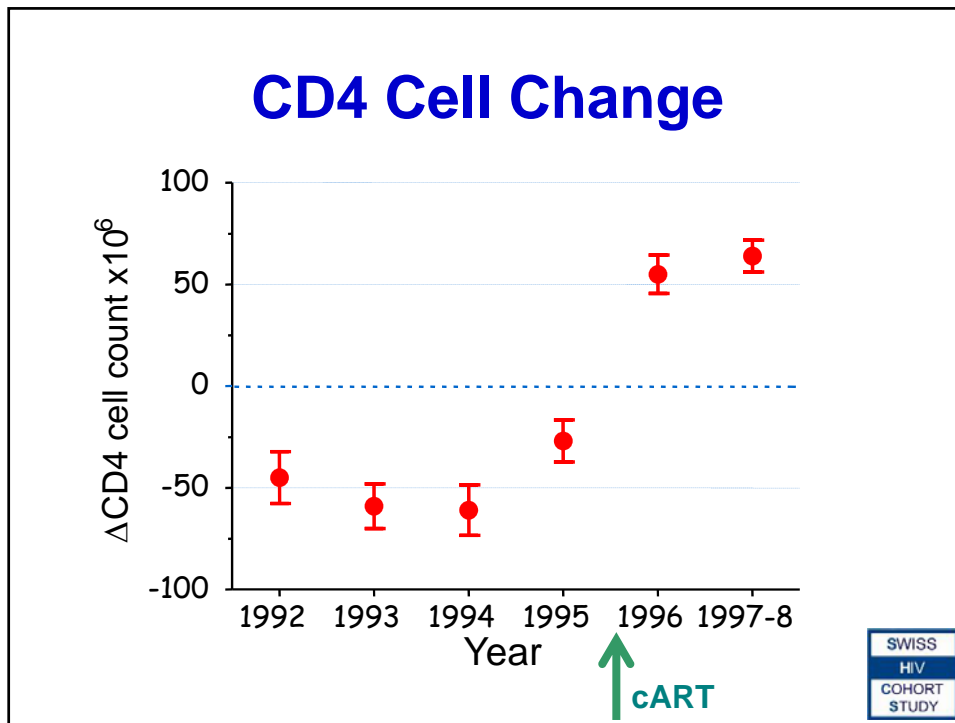
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1058-4838/2005/4005S3-0001



Epidemiology of OIs in HIV patients

Trend in use of ART





Resolution of OIs

For OI where no specific treatment is available

Kaposi sarcoma, PML

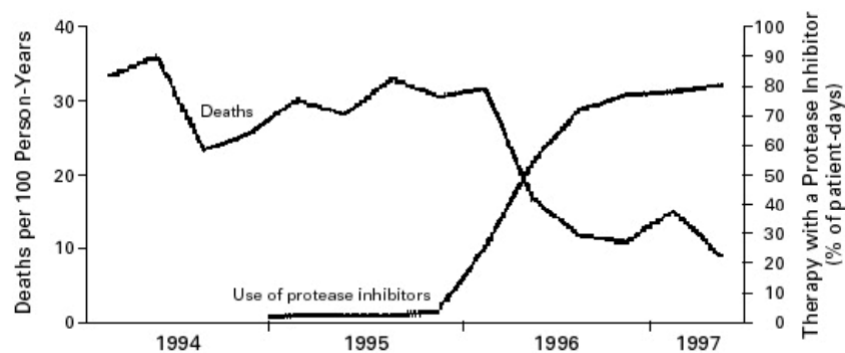
Cryptosporidiosis, microsporidiosis

Acute OI and immediate ART

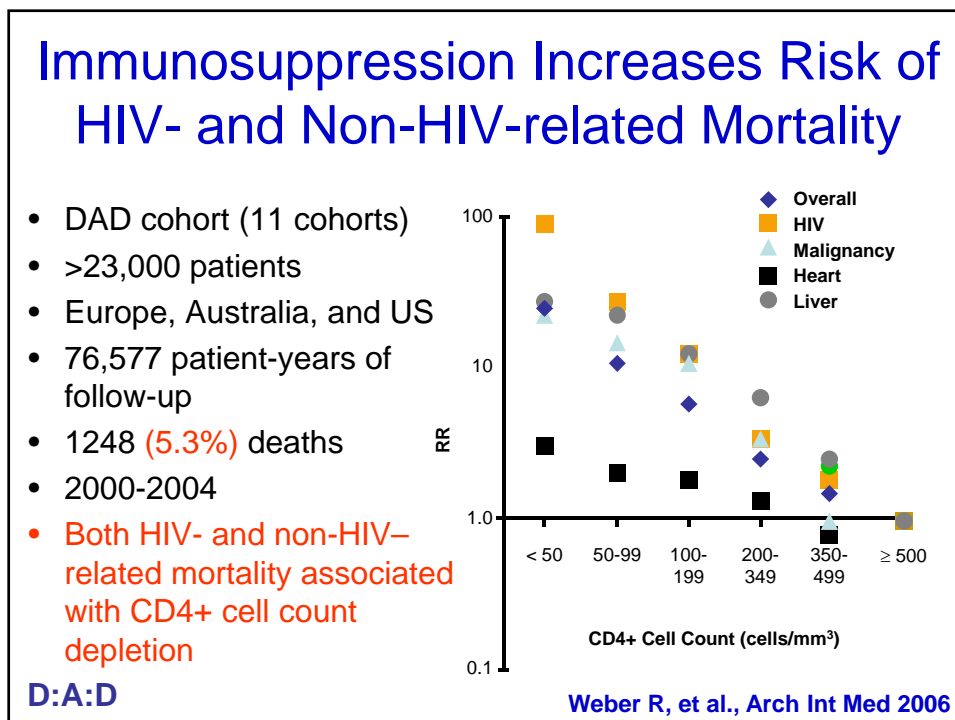
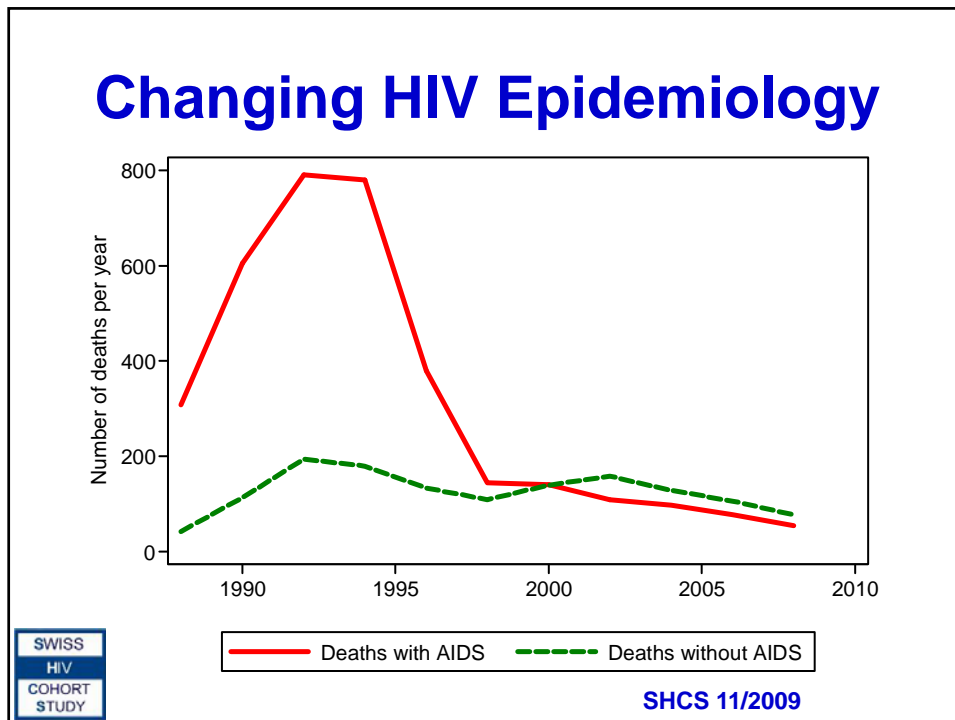
- Improved outcome of OI
- Reduction in risk für a second OI

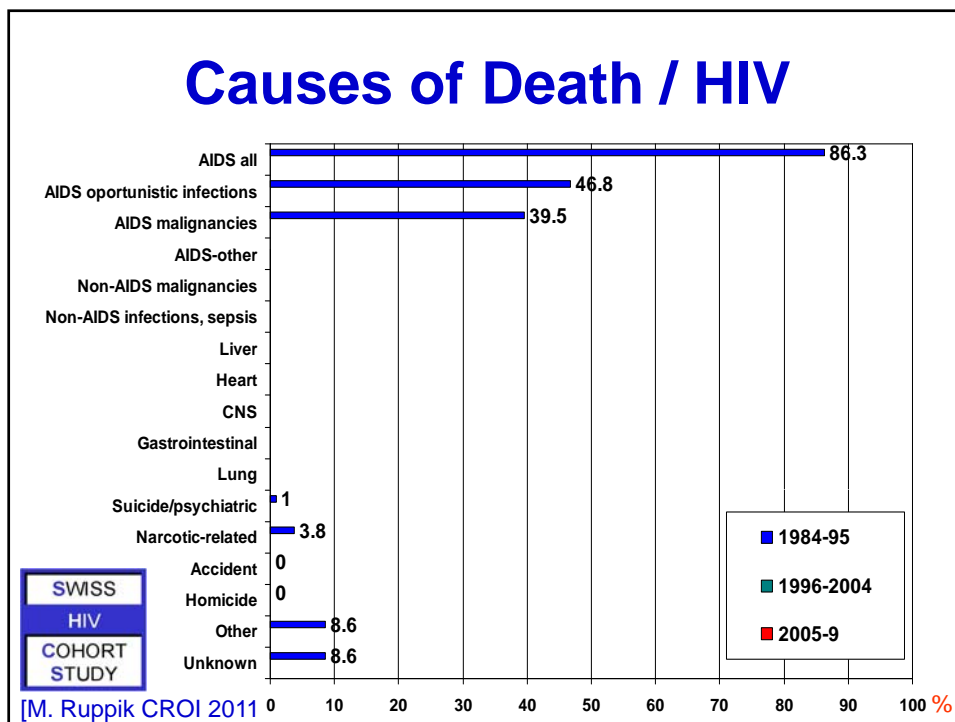
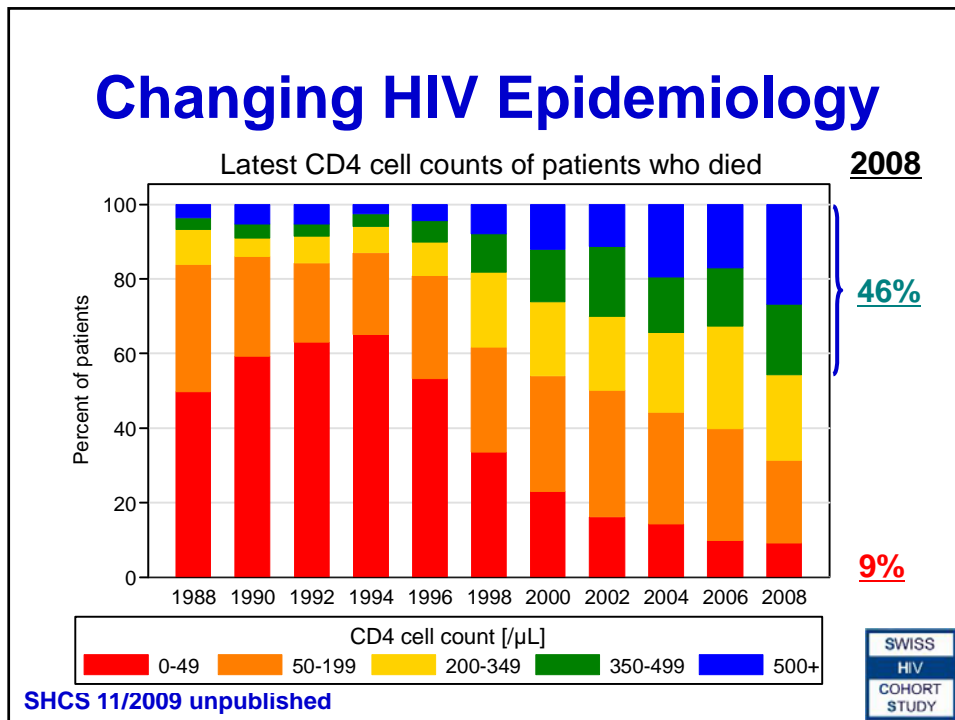
Declining mortality

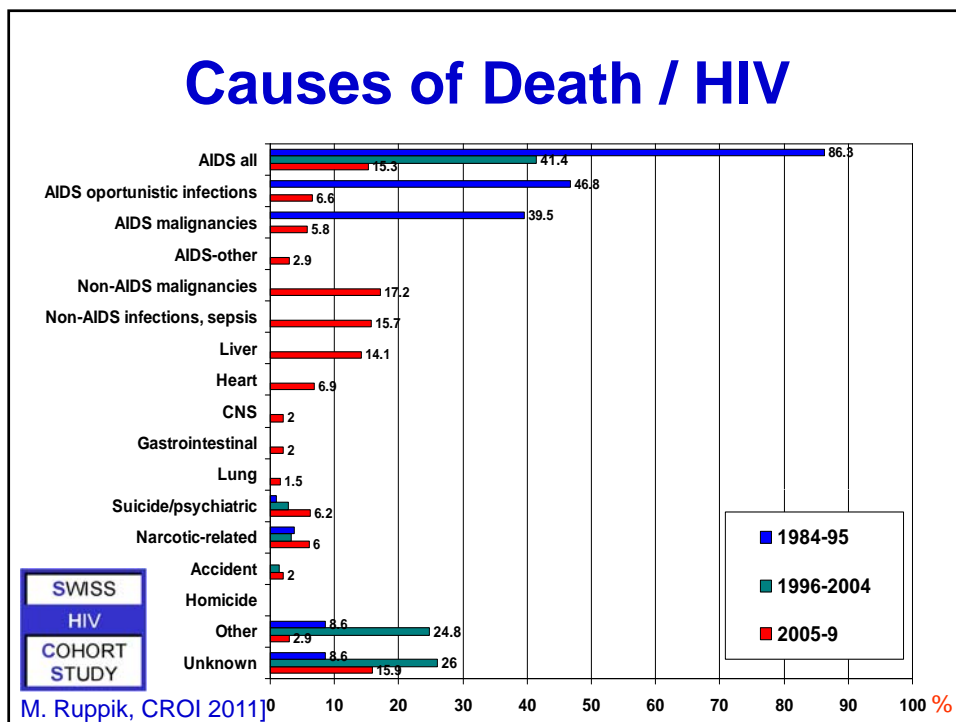
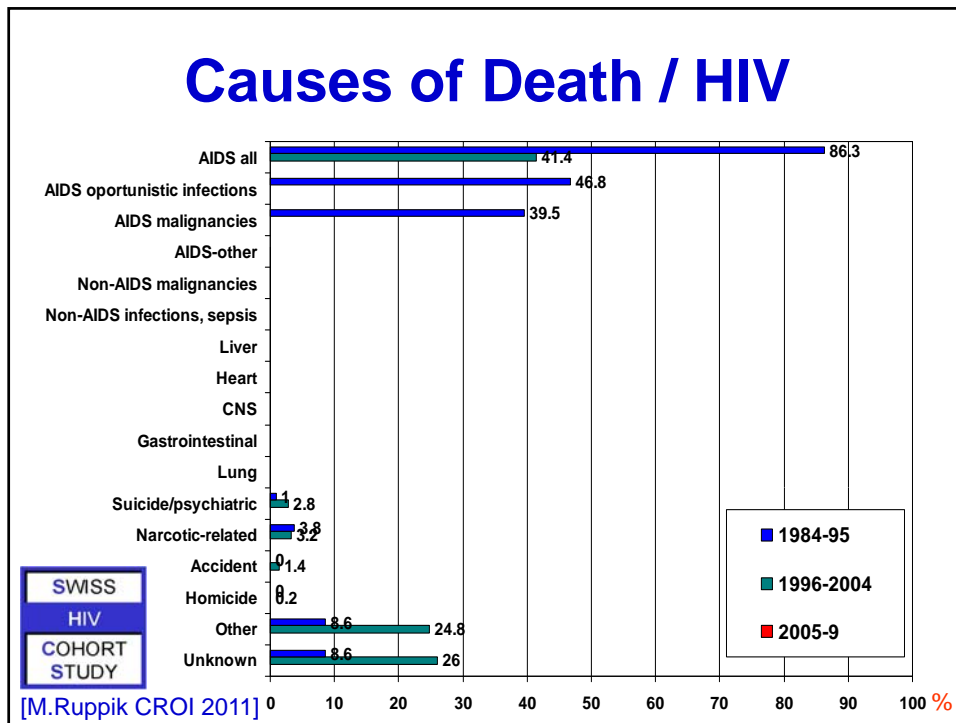
1255 patients
at least one CD4+ count below 100 cells per cubic millimeter,
January 1994 through June 1997.



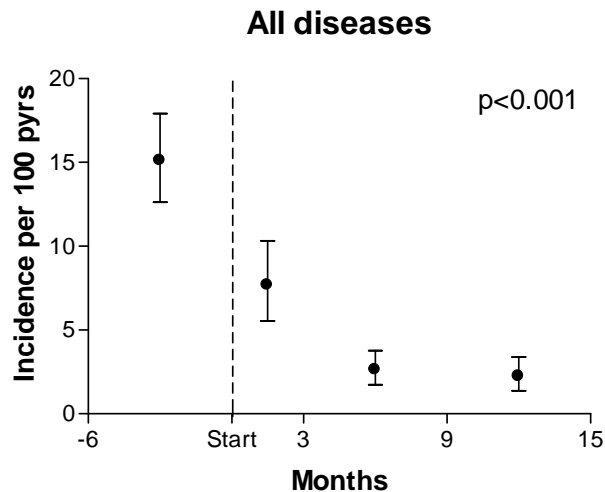
Pallela FJ Jr et al. N Engl J Med 1998; 338: 853-60







Efficacy of ART: All diseases



Ledergerber B et al. JAMA 1999; 282:2220-26



OI: Success of ART

- Prevention of OIs (< 200 cells/ μ l, partially > 200 cells/ μ l)
- Resolution or improvement of OIs
 - In OIs where no specific treatment is available
- Reduction of mortality
- Reduction of morbidity
 - opportunistic infections
 - Non AIDS defining comorbidities

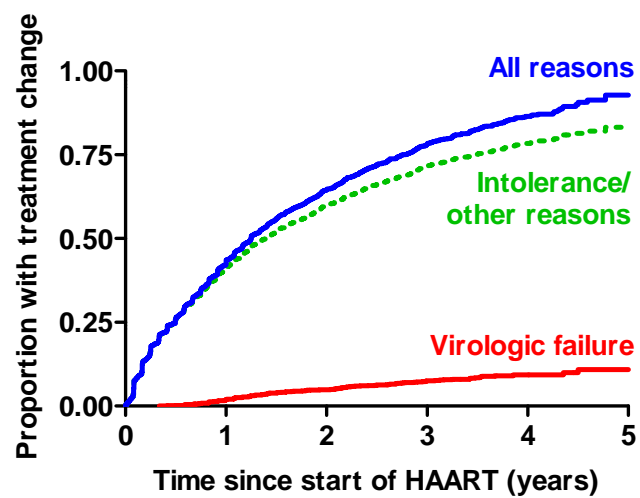
Opportunistic infections in HIV patients still a matter of concern?

Treatment naïve Persons: Reasons for OI

- Persons unaware of their HIV infection
 - present with OI as initial indicator
- Persons aware of their HIV infection
 - do not take ART due to psychosocial or economic factors

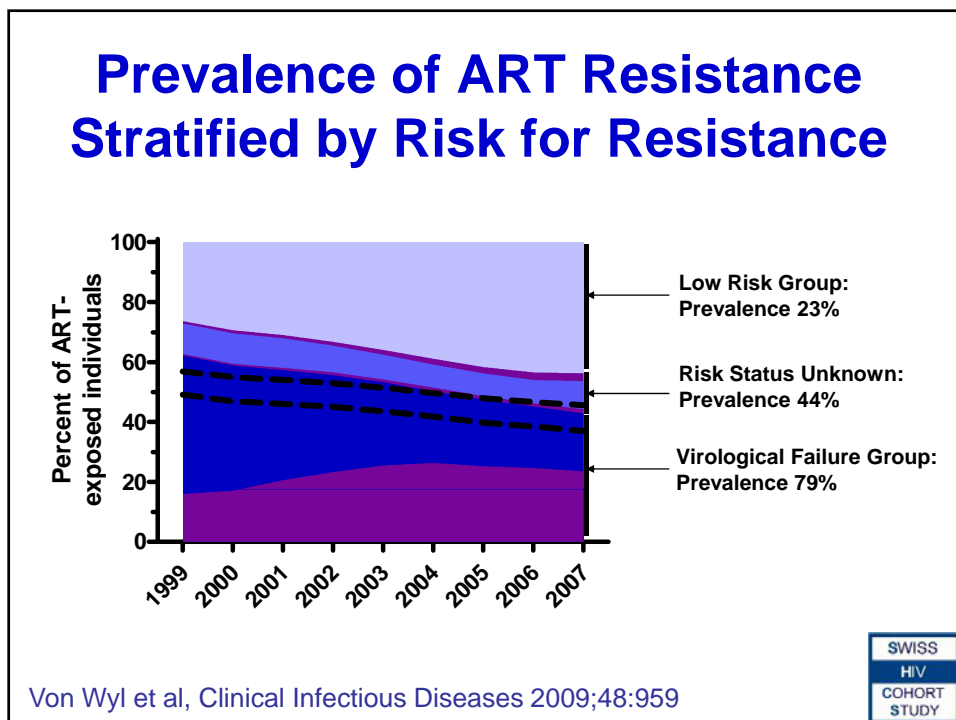
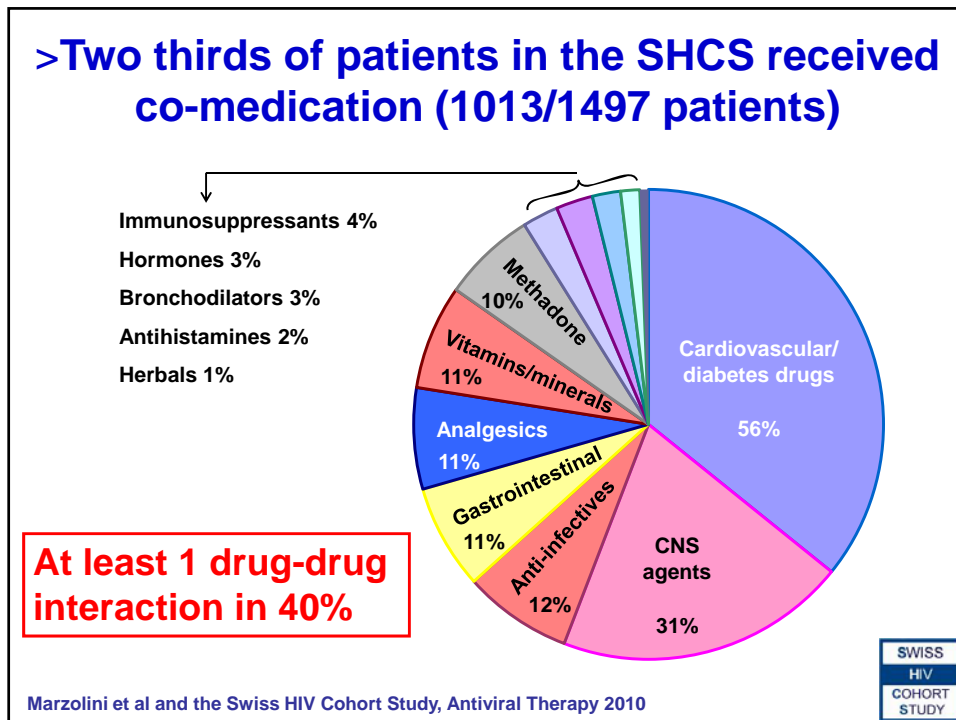
Treatment experienced persons: Reasons for OI ?

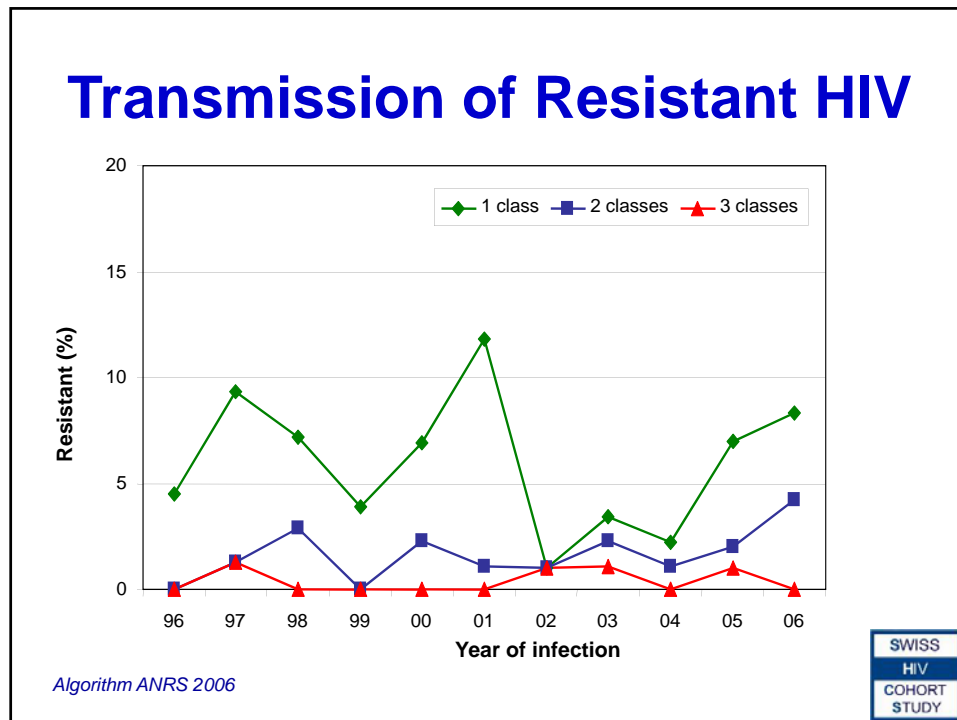
Reasons for Treatment Change



SWISS
HIV
COHORT
STUDY

SHCS 11/2009 unpublished

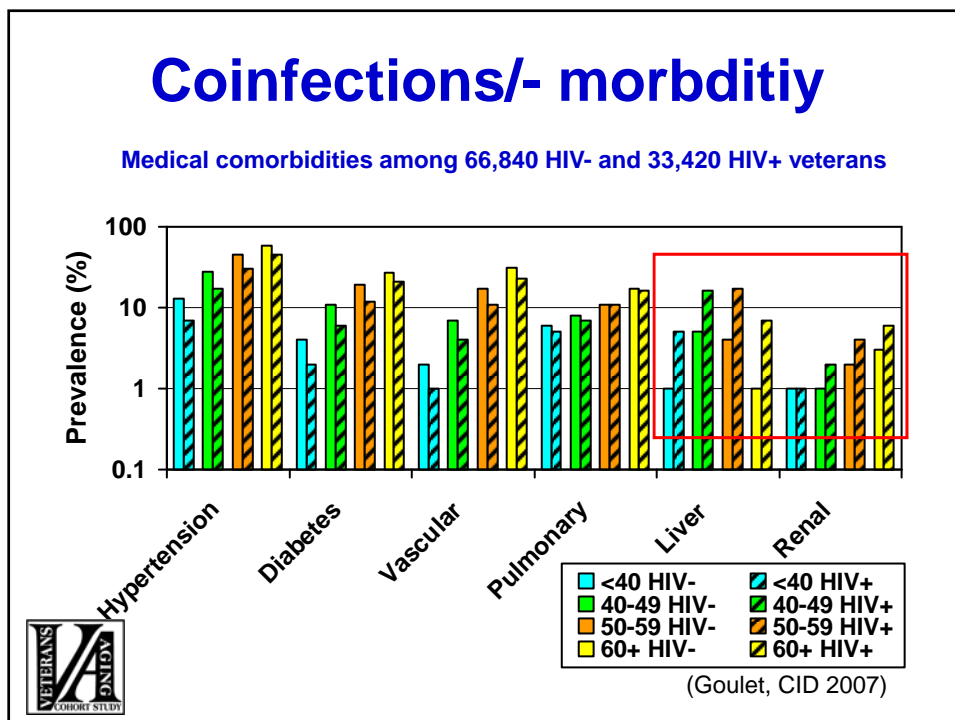
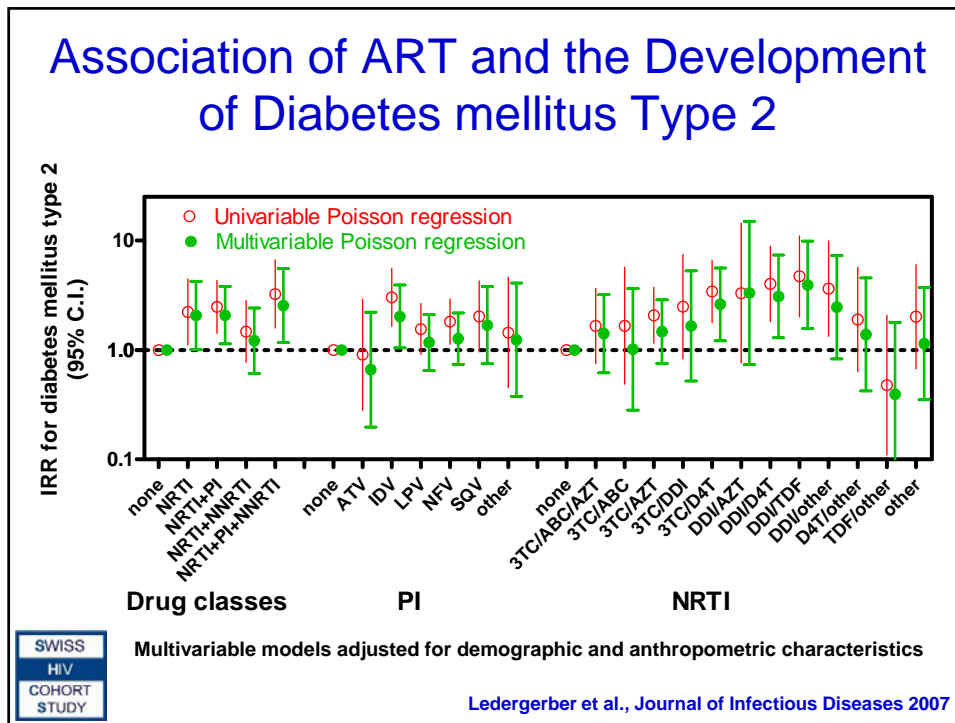




Treatment experienced Persons: Reasons for OI

- Persons with prescribed ART
 - Inadequate immunologic or virologic response
 - Poor adherence
 - Pharmacokinetics
 - Drug resistance

Other reasons?



Treatment experienced Persons: Reasons for OI

- **Persons with prescribed ART**
 - Inadequate immunologic or virologic response
 - Poor adherence, pharmacokinetics
 - Drug resistance
 - Long-term toxicity
 - No reduction in risk of comorbidity
 - Difficult in case of coinfections
 - Access to ART limited and expensive

Considerations on Opportunistic infections and ART

Case 1

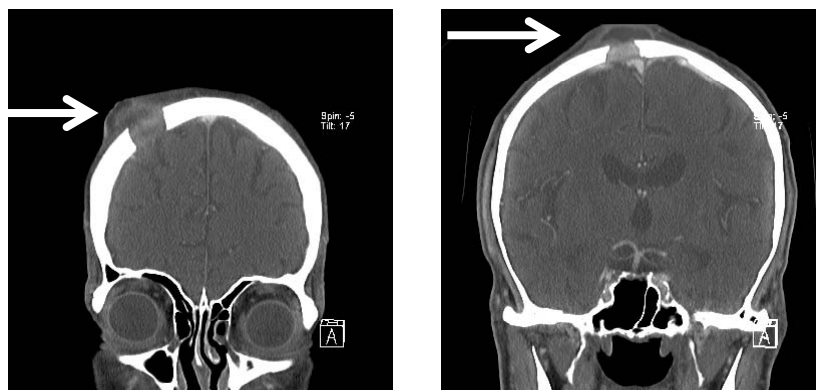
Case 1 – 55-year-old Swiss

- HIV-infection
- Living in Thailand since 2 years
- Previously on ART, stopped therapy 6 month ago
- Presented with weight loss of 14 kg, oral thrush
- Intermittent fever? / No fever
- CD4 cell count 1 cell/ μ L
- HIV-1 RNA 183,000 copies/ml

Case 1 – 55-year-old Swiss

- Appears ill, 56 kg, BMI 16.7 kg/m²
- T 36.0° C, P 83/min, BP 155/92 mm Hg
- Oral thrush, two “fluctuating” tumours on skull
- Haemoglobin 9.0
- Leukocytes 3280
- Thrombocytes 235,000
- C-reactive protein 117 mg/l

Case 1 – 55-year-old Swiss



Case 1 – 55-year-old Swiss

Diagnostic step(s)?

Case 1 – 55-year-old Swiss

Diagnostic step(s)?

- Biopsy: Granular inflammation, culture negative

Case 1 – 55-year-old Swiss

Diagnostic step(s)?

- Biopsy: granular inflammation, culture negative
- **Blood cultures: *Salmonella* Group B**
- *Bartonella henselae* serology and PCR (from skull abscess) negative

Discussion – Case 1

- **Diagnosis**
 - Non-typhoidal *Salmonella* bacteraemia with extra-intestinal focal infection
 - **Remarkable**
 - Afebrile patient at presentation
 - Atypical clinical presentation of non-typhoidal salmonellosis
- **Perform blood cultures in severely ill and immuno-deficient patients also in the absence of fever**

OI AND ART: Considerations

- Atypical presentation of OI

Case 2

Case 2 - 33 year-old

Formerly healthy female truck driver

Recurrent abscesses in the left groin
Candidiasis in mouth

HIV Diagnosis november 2003,
CD4 10 cells, 630'000 HIV-RNA
ART Start

Case 2

Day 8: Candidiasis, small lymphnode on left neck

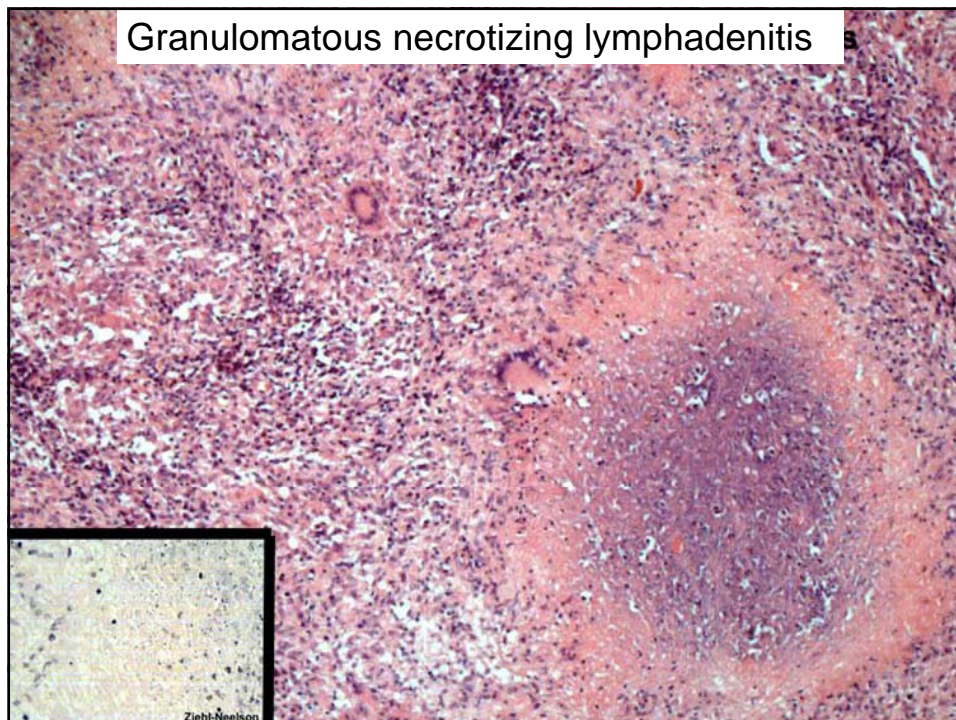
Day 10: Increasing swelling of lymphnode

Day 25: Painful swelling of Lymphnode. Erythema and nodules on wrist, arm and Leg.



Case 2 - Discussion

- **Diagnosis**
 - Mykobacterium avium lymphadenitis with erythema nodosum
 - HIV Infection
- **Remarkable**
 - Clinical presentation with IRIS
 - Worsening of clinical presentation when initiation ART
- **Diagnostik steop**
 - Biopsy of lymphnode



IRIS

- Adverse clinical phenomena following immune reconstitution
 - Previously latent infections are unmasked
 - Pre-existing opportunistic infections deteriorate
 - Other immune phenomenon
- Opportunistic infections (fever and worsening of OI)
- Hepatitis virus infections
- Sarcoidosis [1]
- Rheumatic complications [2]
- Lymphoid interstitial pneumonitis [3]

1, Foulon G et al. Clin Infect Dis 2004;38:428-25
2, Calabrese LH et al. Semin Arthritis Rheum 35;166-74
3, Ingiliz P et al. HIV Medicine 2006;7:411-4

OI and ART: Considerations

- Atypical presentation of OI
- **Extuberant Inflammatory reaction**

Initiation of ART in the Setting of an acute OI

Immediate ART for acute OIs

Start now

Acute OI where no
effective treatment
is available.

Prevention of a second OI



Start later

Drug toxicities,
Additive toxicities
Potential drug interactions
between OI therapy and ART
Potential for IRIS

When to start ART?

- **Considerations:**
 - Availability of effective therapy for OI
 - Risk of drug interactions
 - Overlapping drug toxicities
 - Risk for and consequences of IRIS
 - Adherence to ART

Case 2

- Mycobacterium avium lymphadenitis with erythema nodosum

Failure of ART ?

OI: Initiation of ART

OI < 12 Weeks on ART

Subclinical infections unmasked by immune-restoration

- No failure of ART
- Treatment of OI
- Adjunctive therapy with steroids in case of IRIS
- Continue ART

When to start ART?

As soon as possible

- Cryptosporidiosis
- Microsporidiosis
- PML
- Kaposi Sarcoma

Wait for reponse of OI

- Tuberculosis
- Pneumocystis carinii
- MAC
- Cryptococcosis

Case 3

Case 3 – 33-year-old Brazilian

- HIV infection, CD4 cells $<100/\mu\text{L}$, HIV RNA 65,000 copies/ml
 - Cerebral toxoplasmosis
 - Cytomegalovirus colitis
 - Syphilis II
- April 2005 start ART – 13 months thereafter
 - increasing **sensory loss in the left distal leg**
 - progressive foot drop
 - various **painful erythematous nodules on legs, arms and chest**
 - malaise and **recurrent fever**

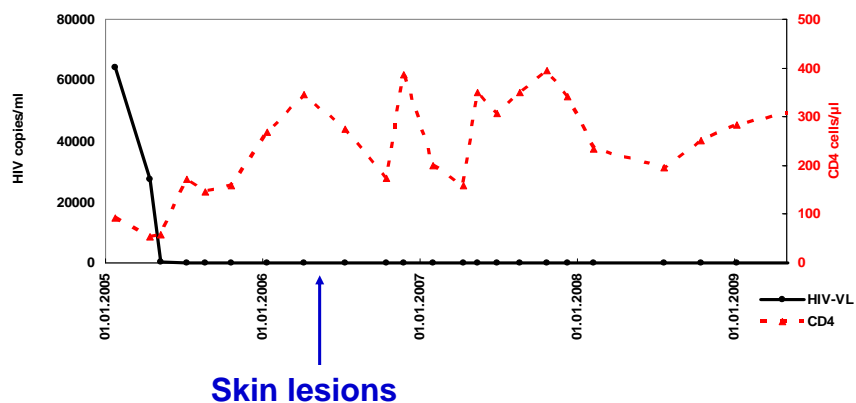
BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

Case 3 – 33-year-old Brazilian



BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

Case 3 – 33-year-old Brazilian



Case 3 – 33-year-old Brazilian

Differential diagnosis?

- Erythema nodosum
- Kaposi sarcoma
- Leishmaniasis
- Syphilid
- Other infection (fungal, mycobacterial)?

BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

Case 3 – 33-year-old Brazilian

- Diagnostic step?

BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

Case 3 – 33-year-old Brazilian

Skin biopsy

- Detection of acid-fast bacilli
- PCR positive for mycobacteria
- Sequencing: *M. leprae*

BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

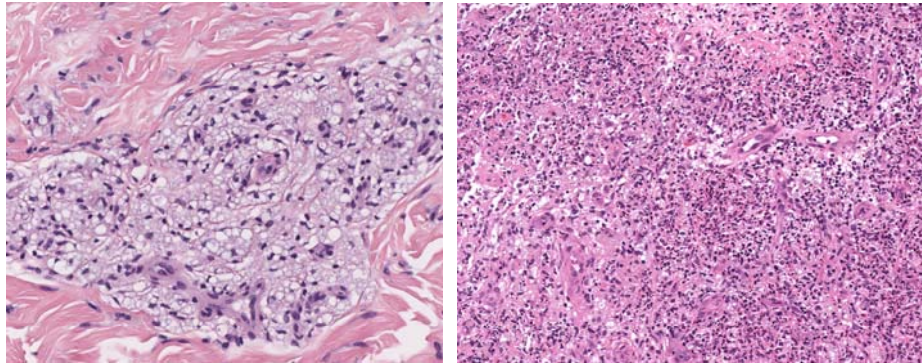
Case 3 – 33-year-old Brazilian

- ART
- Treatment of leprosy
 - Rifabutin 600 mg/month
 - Clofazimine 300 mg/month, and 50 mg/d
 - Dapsone 100 mg/d
- Prednisone
- Several relapses
- Thalidomide



BMJ Case Reports 2009 [doi:10.1136/bcr.05.2009.1904]

Case 3 – 33-year-old Brazilian



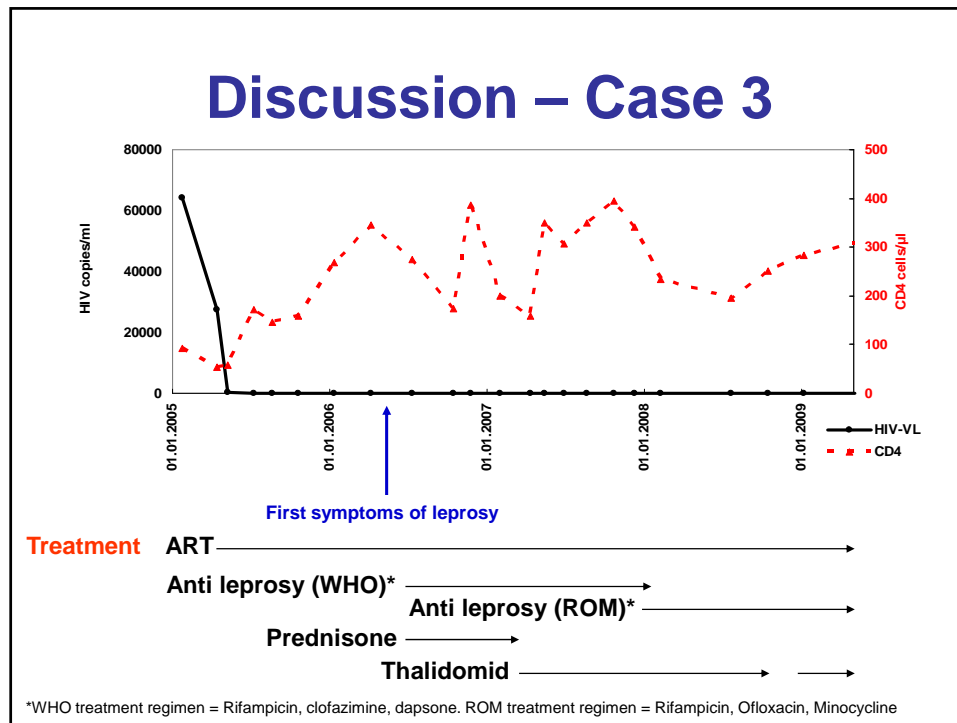
Left: Histology of a nodule from the left leg (2006) showing infiltrations with histiocytes in the nerve sheath without granulomatous reaction.

Right: Histology of an erythema nodosum leprosum nodule on the left hand (2009) showing a polymorphonuclear leukocyte inflammatory infiltrate in the deeper layer of the dermis and subcutis.

[BMJ Case Reports 2009 \[doi:10.1136/bcr.05.2009.1904\]](https://doi.org/10.1136/bcr.05.2009.1904)

Discussion – Case 3

- **Diagnosis**
 - Lepromatous leprosy with erythema nodosum leprosum as **immune reconstitution inflammatory syndrome (IRIS)** 1 year after initiation of antiretroviral therapy
- **Course of CD4 cell count**
 - Figure
- **Consider diagnosis in persons from endemic areas**
- **Unusual**
 - IRIS >1 year after start of ART



OI: Initiation of ART

OI > 12 Weeks on ART, VL not detectable,
 CD4 cells > 200 cells/microliter

- Treatment of OI
- Continue ART
- Adjunctive therapy with steroids in case of IRIS (rare)
- Eventually modify ART

Remarkable features of OI

Case 4

Case 4 – 31-year-old Nigerian

- **Diarrhea**, vomiting, weight loss 25 kg within 5 months, **intermittent fever**, night sweats, cervical tumour, **productive cough**
- Appears ill, T 39.4° C, BP 100/80 mm Hg, P 104/min
- Cervical tumour 5x8 cm, **multiple skin lesions** (→ **figure**)
- Otherwise physical examination unrevealing
- HIV Diagnosis since 2 Years, on ART

Case 4 – 31-year-old Nigerian



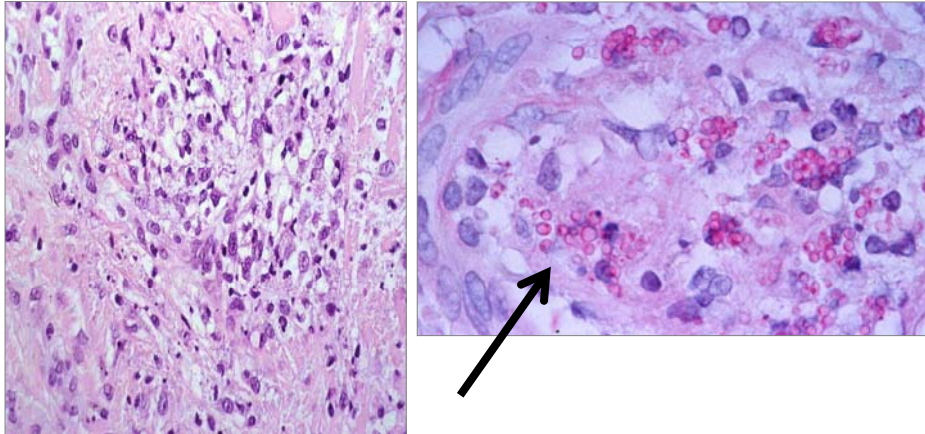
Case 4 – 31-year-old Nigerian

- CD4 lymphocytes 2 cells/ μ l; HIV-1 RNA 130'000 copies/ml
- Haemoglobin 6.5 g/dl; Malaria negative; liver enzymes, LDH, CRP all mildly elevated
- Blood cultures: bacteria negative; growth of *Mycobacterium avium complex*
- Cryptococcal antigen (blood) negative
- Microbiology/parasites sputum and stool negative
- Chest x-ray: normal
- Chest and abdominal CT scan: normal except cervical lymphadenopathy
- Lymph node biopsy: Granulomatous inflammation; bacteria and mycobacteria negative

Case 4 – 31-year-old Nigerian

- Diagnostic step?

Case 4 – 31-year-old Nigerian



Skin biopsy and culture

Discussion – Case 4

- **Diagnosis**
 - African histoplasmosis
(*Histoplasma capsulatum* var. *duboisii*)
 - **Remarkable**
 - Clinical presentation suggested TB
 - Skin lesions suggested Kaposi's sarcoma
 - **Diagnostic procedure**
 - Skin biopsy, fungal culture of skin biopsy
- **Consider endemic pathogens and Dual infections**

OI: Initiation of ART

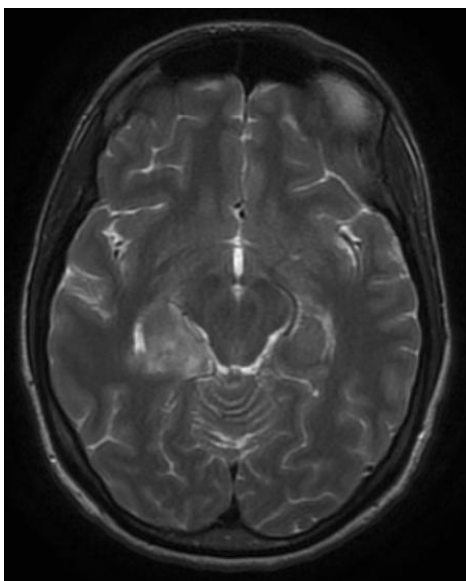
- **Persons with virologic failure**
 - Treatment of OI
 - Resistance test
 - Necessity to modify ART

Case 5

Case 5 – 75-year-old Swiss

- Hospital admission due to indirected dizziness and headache. Uncertainty when walking.
- At presentation: hemianopsia to the right

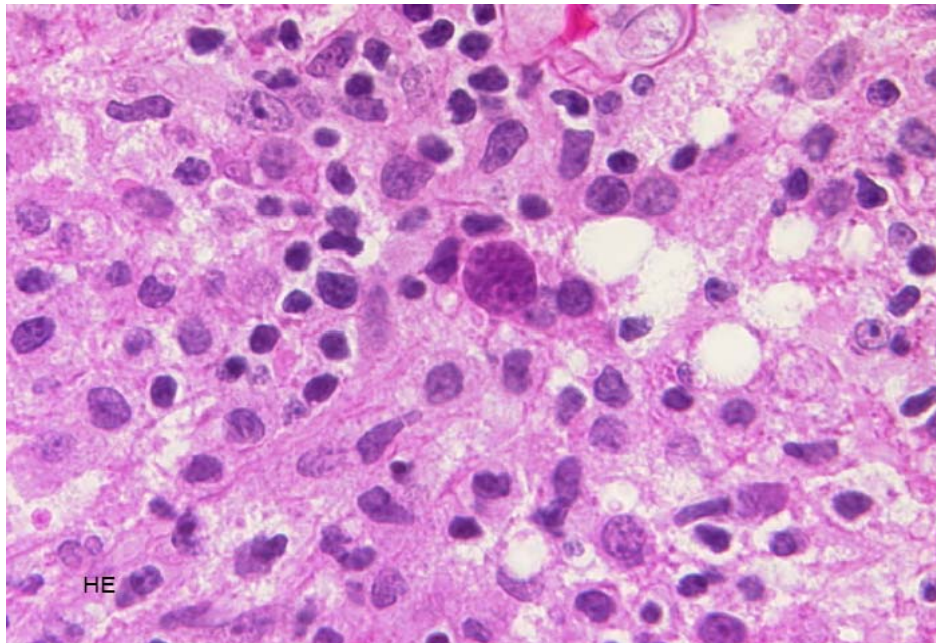
Case 5 - MRI



Space consuming lesion in MRI in
Cuneus

Case 5

- Diagnostic step?

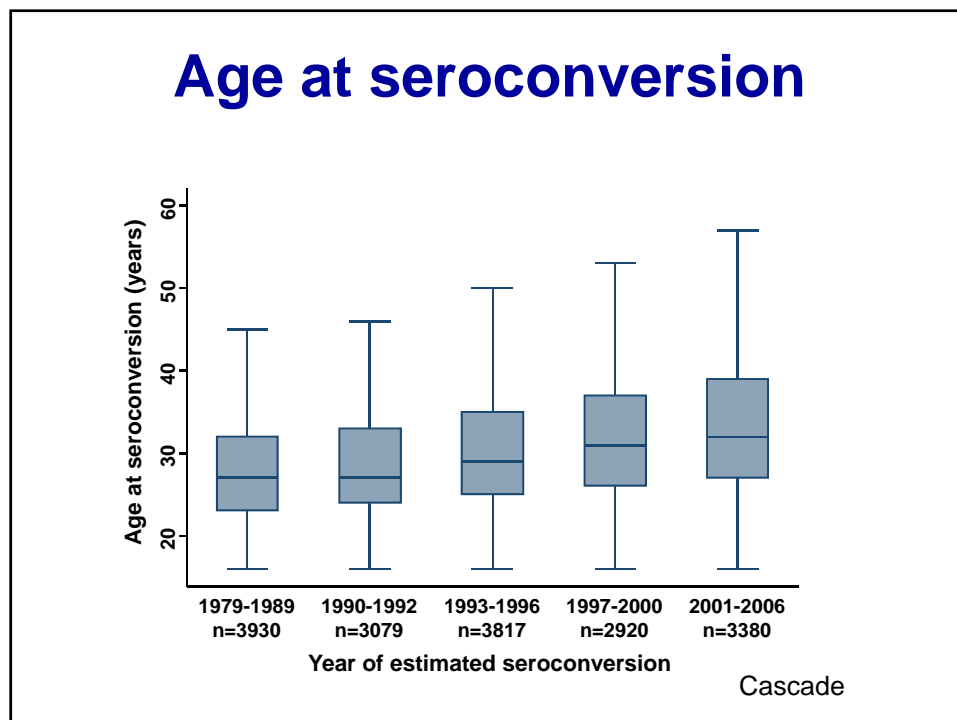
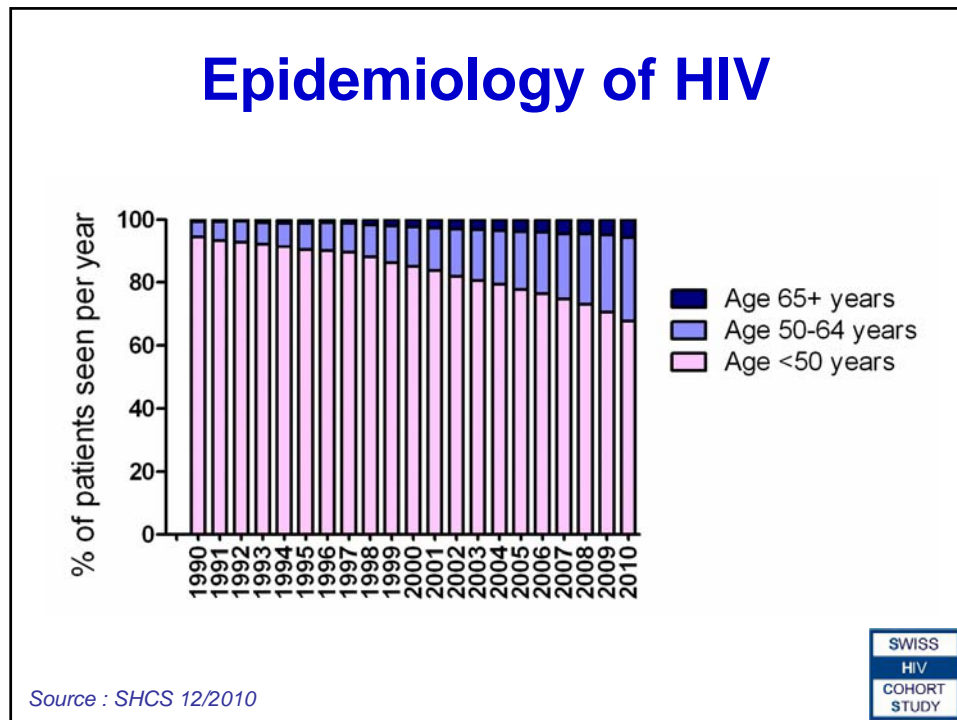


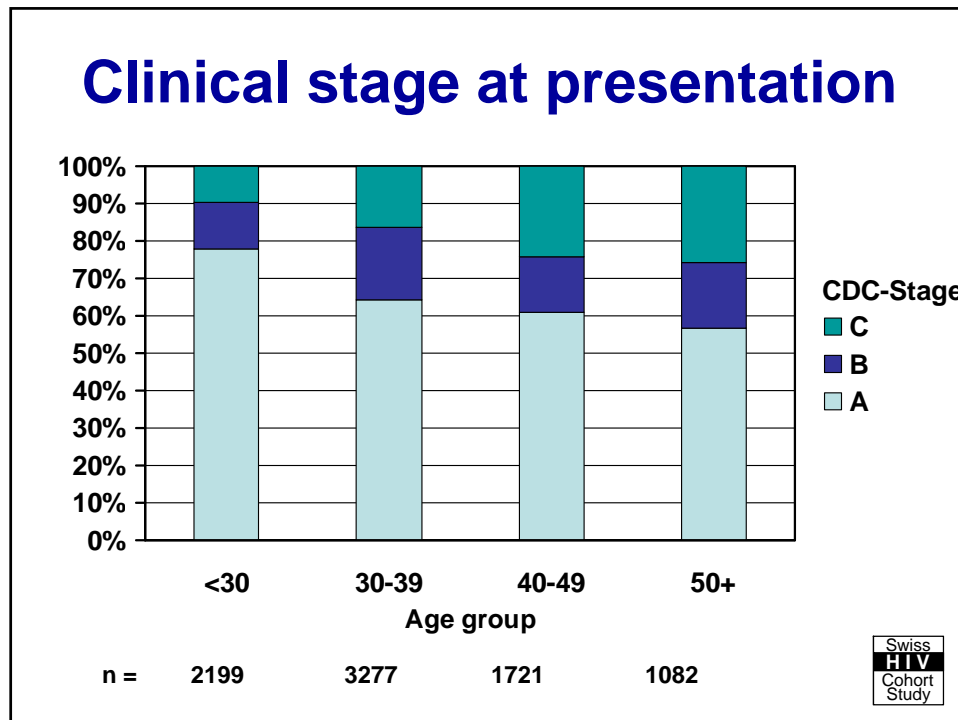
Case 5

- HIV-1 positive
 - CD4 cell count 17 cells/ μ l (6%)
 - HIV-1 RNA: 190'000 copies/ml

Case 5- Discussion

- **Diagnosis**
 - Cerebral Toxoplasmosis
 - HIV Infection
 - **Remarkable**
 - Clinical presentation suggested tumor or ischemia
 - Think HIV
 - **Diagnostisc Step**
 - Typical radiologic Features, leukozytopenia
 - Positive serology for toxoplasmosis
- Delayed presentation for care among older individuals



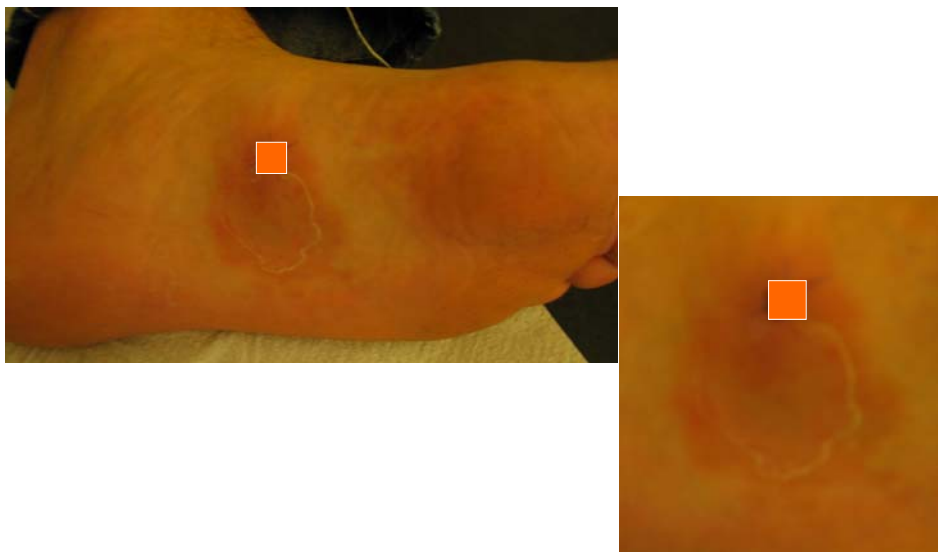


Case 6

Case 6 – 33-year-old Swiss

- HIV-infected, on ART, CD4 cells 283/ μ L, HIV RNA not detectable
- Intermittent fever, since more than 8 weeks, up to 40° C
- Intermittent macular exanthema
- Difficulties to concentrate
- More recently flu-like symptoms
- At presentation: afebrile, no generalized exanthema, skin lesion on foot (\rightarrow figure), physical examination unrevealing, no neurological deficits

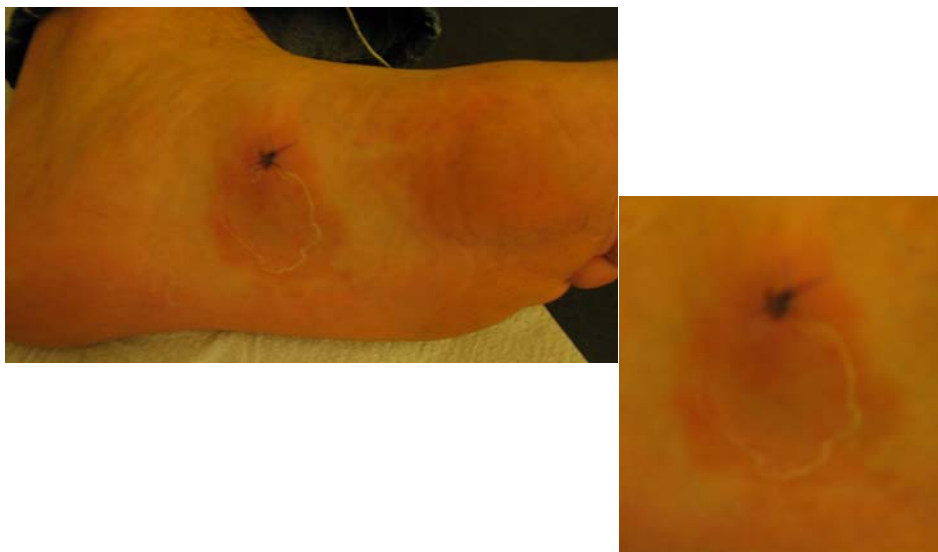
Case 6 – 33-year-old Swiss



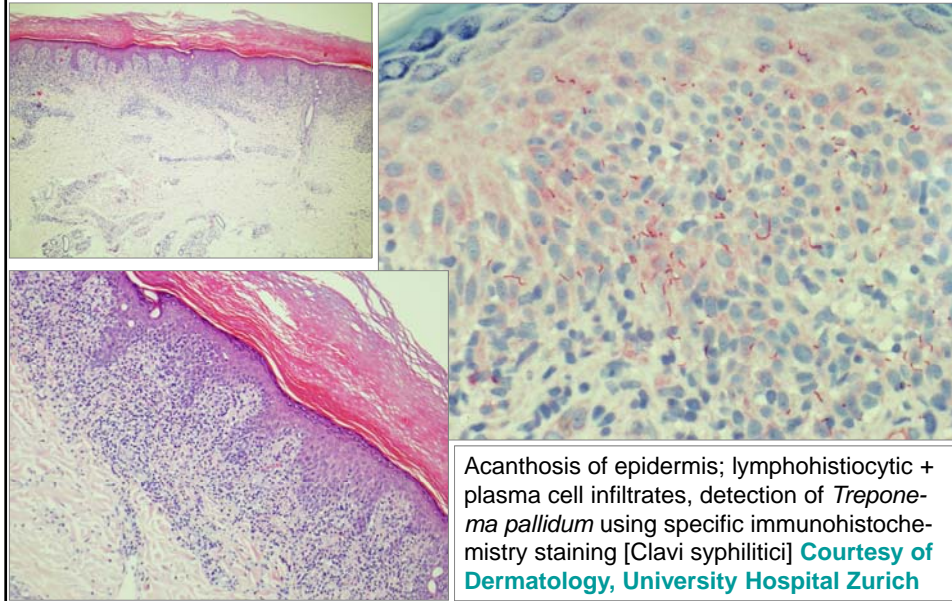
Case 6 – 33-year-old Swiss

- Diagnostic step?

Case 6 – 33-year-old Swiss



Case 6 – 33-year-old Swiss



Case 6 – 33-year-old Swiss

- Serum
 - VDRL 1:8
 - *Treponema pallidum* Haemagglutination Assay (TPHA) 1:40,960
- Cerebrospinal fluid
 - 3 cells
 - No detection of *T. pallidum* antibodies

Discussion – Case 6

- **Diagnosis**
 - Syphilis stage II
 - **Remarkable**
 - Syphilis as cause of fever of unknown origin
 - No history of sexual risk
- Think syphilis
- Sexual history not reliable

Case 7

Case 7 – 56-year-old Swiss

- HIV infection; bisexual behaviour
- Nadir CD4 cells 38/ μ L; on ART since 11/2007; CD4 cell increase up to 107 (12/2009)
- 10/2009 hospitalized
- Fever, diarrhea, collapse
- T 38.6° C, splenomegaly (21.5 x 12.5 cm)
- CD4 34/ μ L, haemoglobin 6.6 g/dl
- Comprehensive evaluation, incl. CT scans, upper endoscopy, colonoscopy (biopsies), bone marrow: no diagnosis (except detection of *C. difficile*)

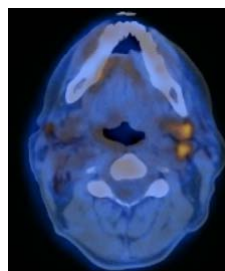
Case 7 – 56-year-old Swiss

- 02/2010 – after temporary improvement – re-hospitalization: fever up to 39.5° C, fatigue, diarrhoea, on ART
- T 37.4° C, BP 92/62 mm Hg, P 104/min, BMI 25.2 kg/m², cervical, axillary lymphadenopathy (1 cm), liver 12 cm, splenomegaly
- CD4 cells 61/ μ l, viral load not detectable
- Haemoglobin 7.6 g/l, leukocytes 8710, thrombocytes 110,000
- CRP 228 mg/l, creatinine 303 μ mol/l, ferritin 5739 μ g/l, liver enzymes normal

Case 7 – 56-year-old Swiss

- 02/2010
- Comprehensive evaluation including imaging
- **PET scan:** FDG uptake in cervical, supra- and infra-clavicle and axillary lymph nodes (up to 1 cm), single pelvis lymph node
- Virology negative except EBV DNA 916 copies/ml
- Microbiology and mycobacteriology negative except *C. difficile*
- Serologies: negative

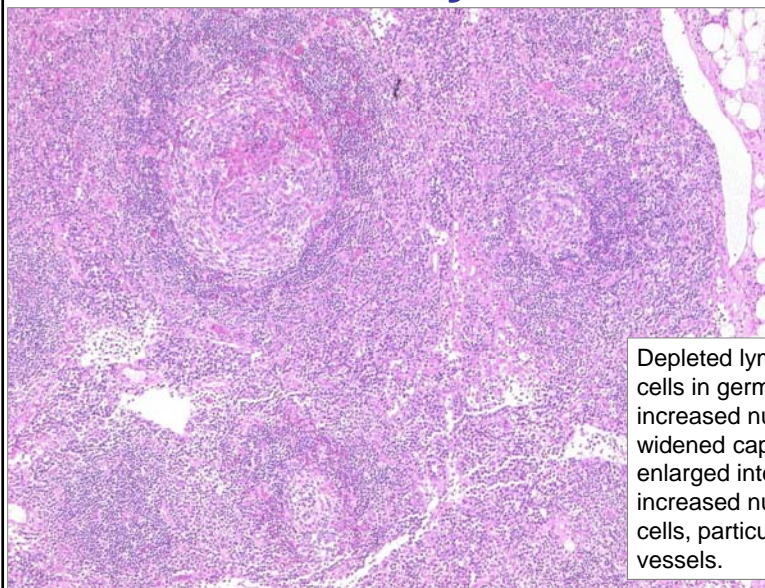
Case 7 – 56-year-old Swiss



Case 7 – 56-year-old Swiss

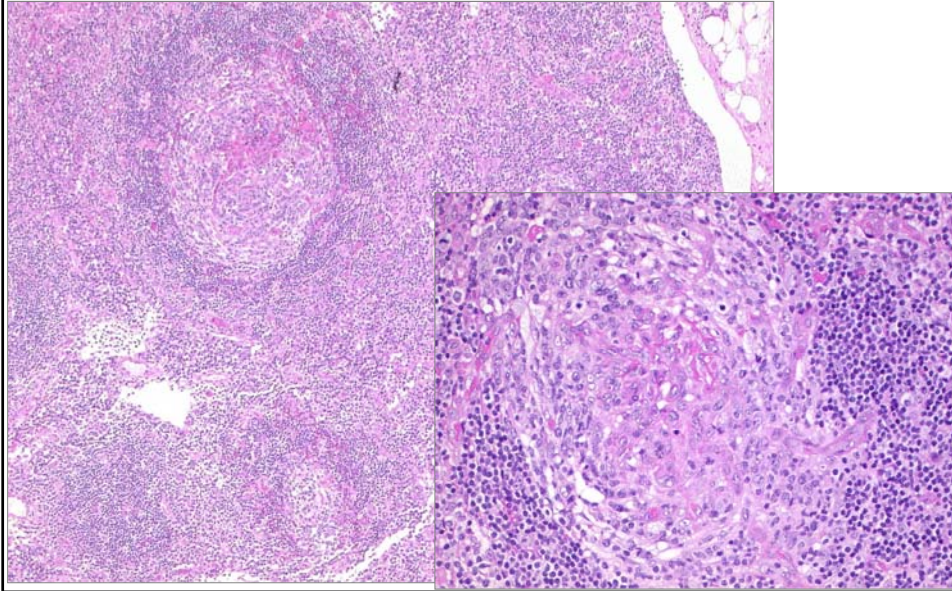
- Diagnostic step?

Case 7 – 56-year-old Swiss



Depleted lympho-epithelial cells in germinal centre; increased number of slightly widened capillaries in the enlarged interfollicular zone; increased number of plasma cells, particularly around vessels.

Case 7 – 56-year-old Swiss



Case 7 – 56-year-old Swiss

- Biopsy: Multicentric Castleman's disease
- Plasma: **Human herpes virus 8: 31,111 DNA copies /ml**
- ART continued
- Rituximab, etoposid

Discussion – Case 7

- **Diagnosis**
 - Multicentric Castleman disease
- **Of note**
 - No Kaposi's sarcoma
- **Clues**
 - Lymph node biopsy
 - Detection of HHV-8 DNA in plasma and lymph node biopsy

Conclusions

Case Presentations

- 1 Non-typhoidal *Salmonella* bacteremia with extraintestinal septic foci
- 2 Mycobacterium avium lymphadenitis
- 3 Lepromatous leprosy with erythema nodosum leprosum presenting as IRIS
- 4 African histoplasmosis and MAC
- 5 Cerebral toxoplasmosis
- 6 Syphilis II (fever)
- 7 Castleman disease

OI – Conclusions (1)

- Decrease in incidence because of ART
- Work-up initially directed toward infections
 - Occult opportunistic infections
 - Geographic prevalence of pathogens
 - Sexually transmitted infections
 - TB
- Increase of non-HIV-related malignancies

OI– Conclusions (2)

- IRIS increasing
- New drug toxicities
- Non-AIDS malignancies increasing
- More sexually transmitted infections
- More travel-associated diseases
- Endemic infections in migrants and VFR
(*Visiting Friends and Relatives*)

OI – Key information

- Clinical manifestations
- CD4 lymphocyte stratum
- Epidemiology
 - Relative frequencies of causes
 - Exposition
 - Geographic setting, patient's origin, (long-term) travel history
 - Behaviour (Sexually transmitted infections; illicit drug use; etc.)
 - Nosocomial
 - Other: Animal, human, food, environment
- Co-morbidity, co-infections
- Medication
 - Toxicity
 - Immune reconstitution inflammatory syndrome (IRIS)

Acknowledgements

- Patients
- Colleagues of the ID Division in Zurich
- Swiss HIV Cohort Study

