Late diagnosis of HIV-infection

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Topics

• Definition
• Epidemiology
• Management
  - acute complications
  - initiation of antiretroviral therapy
  - immune reconstitution inflammatory syndrome (IRIS)
• Prevention
Late diagnosis of HIV-infection

- diagnosis of HIV-infection
  - concomitant or close in time with opportunistic complication or
  - with a low CD4-cell count

- how close in time to clinical event?
- CD4-cells how low?
Late diagnosis of HIV-infection

- diagnosis of HIV-infection
  - concomitant or close in time with opportunistic complication or
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- how close in time to clinical event? 3, 6, 12 months?
- CD4-cells how low? below 200
How frequent is late diagnosis of HIV?

- different cohorts from Italy, France, UK, Germany
- rate of late HIV-diagnosis relatively uniform 25-40%
  - risk factors
    - migrants
    - women
    - age < 30 or age > 50
    - unknown or not reported risk of transmission
    - heterosexual men, living in long-term relationships
Late diagnosis in Germany

- 682 AIDS cases 2003-4
  - >50% no ART before AIDS diagnosis
- CD4 cell count at diagnosis of HIV 1999-2006

ClinSurv-Cohort, RKI 2006; Epid. Bull, April 2005
Late diagnosis in UK

- In GB 14000 cases of newly diagnosed HIV-infection between 1993 and 2002 analyzed
  - 31% below 200 CD4/mcl, positive trend to 25% 2002
  - late diagnoses mainly outside London, higher age, non caucasian origin
  - one year mortality with late diagnosis 14 vs. 1%, down to 9,9 vs. 0,5% 2001

Chadborn AIDS 2005
Are there consequences of late HIV-diagnosis?

- lower rate of viral suppression if ART is started late
- higher rate of opportunistic infections until immune reconstitution is sufficient
- higher rate of adverse effects of ART, especially when initiated with concurrent OI-therapy
- higher rate of immune reconstitution syndrome
- higher mortality
Clinical events after starting HAART by initial CD4-cell count

Eggers, Lancet 2005
Case 1

- 28yo male
Case 1

- Patient with multiple cutaneous nodules, biopsy reveals Kaposi’s-sarcoma, HIV-test positive
- CD4-cell count 230/mcl, Viral load 260,000 copies/ml
- History of repeated deep vein thrombosis and pulmonary embolism - on long-term cumarin-therapy
- Late diagnosis?
- How to treat?
Case 1

- Chance of remission with antiretroviral therapy, so no initial anti-Kaposi therapy
- started on LPV/r +ZDV+3TC, because of case reports of remission of KS in patients treated with PI-based HAART
- Viral load suppressed, lesions blanching
- effective anticoagulation not possible, even with 4 tbls Cumarin/d
- what to do?
Case 1

- Switched to EFV+ZDV+3TC
- good response in CD4-cell-count, good progress with remission of KS
- now for 3 years below limit of detection, complete remission of KS
Case 2

• 43yo male, interstitial pneumonia not responding to empiric therapy with fluorquinolones
• in bronchoscopy Pneumocystis jirovecii, HIV-positive
• rapidly deteriorating respiratory function
• initiate ART concomitant to OI-therapy?
Case 2

- No data if concurrent ART is helpful in acute OIs
- potential for adverse drug reactions, complication clinical management
- therefore rather withhold ART in acute OI?
Case 3

- 28yo female, recently immigrated from Ukraine
- fever, generalized lymphadenopathy and pulmonary infiltrates
- smear positive for AFB
- culture growing *M. tuberculosis*
Case 3

- HIV+, HCV+
- Viral load 120,000 copies/ml, CD4-cell count 80/mcl
- How to treat?
Key questions in HIV-TBC

• how to treat TBC?
• when to start highly active antiretroviral therapy (HAART)?
• which HAART?
  - adverse effects
  - interactions with TB treatment
Which TBC treatment?

• standard regimen
  – 2 months: INH, RIF, EMB, PZA
  – 4 months: INH, RIF
  – directly observed therapy (DOT)

• rifamycins crucial for success of short-term TBC treatment (6 months)

• which rifamycin?
  – rifampicin
  – rifabutin
Rifampin, Rifabutin and PIs

Decrease in Serum-AUC of PIs

![Graph showing decrease in Serum-AUC of PIs with bars for SQV, NLF, IDV, LPV/r, and ATV/r. The graph compares Rifampin (pink) and Rifabutin (yellow).]

CID 1999, 28, 419ff
Rifampin, Rifabutin and NNRTIs

CID 1999, 28, 419ff
What is the best time to start HAART in a patient with HIV/ TBC?
Use of antiretroviral therapy during Tb-infection

• CD4-cell count at diagnosis of Tb
  - <200  start during Tb-therapy
  - 200-350 monitor, start if CD4 declines rapidly
  - >350  monitor,
TB/ HIV Co-Infection: Treatment Considerations

- In patients on ARV therapy, evaluate ARV regimen for interactions with TB drugs
- In ARV-naive patients, avoid simultaneous initiation of treatment for TB and HIV
  - consider delay of ARVs for 4-8 weeks after initiation of TB treatment to avoid overlapping of adverse reactions and paradoxical reactions

DHHS Guidelines July 2005; http://www.aids-etc.org
Case 4

- 44yo male, husband of case 4
- Pleural tuberculosis 2 months after diagnosis of tb in spouse
- HIV+, CD4+ cell count 440/mcl, VL 80,000 copies/ml
- How to treat?
Case 5

- 37yo male patient with fever and enlarging lymph nodes after 2 months of HAART and TBC treatment
- Is this clinical deterioration
- what are the likely causes?
- how to manage?
Case 4

• Likely causes for deterioration
  - resistance (HIV/Tb)
  - non-adherence (HIV/Tb)
  - superinfection
  - immune reconstitution syndrome (IRS)

• How to manage IRS in TB/HIV-coinfection?
  - continuation of TBC treatment
  - consider stop of ART
  - consider cortisone
IRIS

- worsening of preexisting clinical condition after starting ART
- pathogenesis?
- broad spectrum of conditions with IRIS
  - mycobacterial infections
  - PCP, PML
  - infections with Herpesviruses (CMV, VZV, genitale HSV, Kaposi Sarkome)
  - hepatitis B flare
  - cryptococcosis, Histoplasmosis
  - Parvo B19, Graves´disease, lung cancer..
IRIS

- with anti-tuberculosis therapy reported
  - paradoxical reaction with initial or delayed worsening after starting therapy
  - absceding and growing lymphadenopathy
  - enhanced inflammation with tuberculos meningitis, CNS-tuberculomas with focal neurologic deficits treated successfully with steroids
- reversion of specific immunosuppression with initial imbalance?
IRIS-Epidemiology

- Frequency
  - 10-25%
  - in a small London cohort 23%
  - depending on
    prevalence of infections
    CD4-cell-nadir?

- risk factors
  - younger age
  - low CD4-cell count
Pathogenesis I RIS

• pathogenesis largely unknown
• antigen-specific immune responses enhanced or diminished?
the good news.... all is forgotten after 6 months of therapy
the bad news - prevention

• population at risk is difficult to target
  - not a group with „one denominator“: e.g. gay men, drug users
  - risk of infection not acknowledged
Conclusion

- late diagnosis of HIV is common, risk factors are known
- patient populations difficult to target for prevention
- clinical problems in late HIV-diagnosis
  - time to immune reconstitution crucial
  - concurrent management of acute opportunistic infections and ART
  - immune reconstitution syndrome