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Auditorium, Ministry of Health

EACS European AIDS Clinical Society
MEETING

STANDARD of CARE for HIV and COINFECTIONS in EUROPE

Chairs: A. Antinori, A. d’Arminio Monforte, C. Mussini
Late Presentation in HIV infection

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Outline

- Definitions and diagnosis of late presentation
- Consequences of late presentation
- Late presentation across Europe
- Initiatives to reduce late presentation
Outline

- Definitions and diagnosis of late presentation
  - Prevalence of late presentation
  - Consequences of late presentation
  - Initiatives to reduce late presentation
### Many definitions reported

#### Time until first ADE

<table>
<thead>
<tr>
<th>Time until first ADE</th>
<th>Country and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>European survey, 2006</td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>England, 2006</td>
</tr>
<tr>
<td></td>
<td>France, 1998</td>
</tr>
<tr>
<td></td>
<td>Italy, 2005</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>Sweden, 2005</td>
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<tr>
<td></td>
<td>England, 2000</td>
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<tr>
<td></td>
<td>Italy, 2000</td>
</tr>
<tr>
<td></td>
<td>Poland, 2006</td>
</tr>
<tr>
<td>&lt; 8 weeks</td>
<td>Spain, 2002</td>
</tr>
<tr>
<td></td>
<td>Denmark, 2005</td>
</tr>
<tr>
<td>&lt; 1 month</td>
<td>England, 2001</td>
</tr>
<tr>
<td></td>
<td>Italy, 2003</td>
</tr>
<tr>
<td>Concurrent AIDS</td>
<td>Poland, 2006</td>
</tr>
<tr>
<td></td>
<td>England, 2006</td>
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<tr>
<td></td>
<td>France, 2000</td>
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</tbody>
</table>

#### CD4 count

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Country and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 350</td>
<td>England, 2000</td>
</tr>
<tr>
<td></td>
<td>UK 2000, 2005, 2006</td>
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<tr>
<td></td>
<td>France 2006, 2007</td>
</tr>
<tr>
<td></td>
<td>Italy, 2004</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>Spain, 2005</td>
</tr>
<tr>
<td></td>
<td>UK 2004</td>
</tr>
<tr>
<td>CD4 &lt; 50</td>
<td>Poland, 2006</td>
</tr>
<tr>
<td></td>
<td>England, 2006</td>
</tr>
<tr>
<td></td>
<td>France, 2000</td>
</tr>
</tbody>
</table>
Why do we need a common definition?

- To monitor changes in rates of late presentation over time, and assess effectiveness of public health interventions
- To identify risk factors in a common way
- To permit comparisons between countries
- To correlate late presentation rates with country-specific interventions and/or policies for earlier diagnosis
Prevalence of Late Presentation:

**Impact of definition**

Definition based on:
- AIDS
- CD4 < 200 cells/µl
- AIDS and CD4 < 200 cells/µl

*Late Presenter (%), survey timepoint September 2007*

Modified from: Adler A et al. AIDS Care; 2008
Late presentation: Persons presenting for care with a CD4 count <350 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count.

Late presentation with advanced disease: Persons presenting for care with a CD4 count <200 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count.

Antinori, HIV Med 2010
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What are the consequences of starting cART late?

**Short Term**
- Higher risk of mortality in the 1st year
  - ART CC and ART LINC, Lancet 2006; 367: 817–24
- Reduced chance of viral suppression
- Increased risk of hospitalization
  - Sabin CA, AIDS 2004; 18:2145–2151
- More potential drug-drug interaction
  - Rockstroh JK, Antivir. Ther 2010.15 (S1), 25-30
- More likely to have IRIS

**Long Term**
- Increased risk of non-AIDS events
  - Reekie, AIDS. 2011;25(18):2259-68
- Increased risk of neurocognitive impairment
  - Ellis RJ, AIDS 2011;25(14):1747-51
- Potentially increased risk of HIV transmission
- Higher direct cost of care

BHIVA audit: scenario leading to death

n = 387 deaths between October 2004 and September 2005

- Death not directly related to HIV: 31.8%
- Diagnosed too late for effective treatment: 24%
- Under care but had untreatable complication: 15.8%
- Treatment ineffective due to poor adherence: 6.7%
- Chose not to receive treatment: 4.7%
- HIV +ve, irregular care, re-presented too late: 3.4%
- MDR HIV, run out of options: 2.8%
- Successful treatment but suffered catastrophic event: 1.8%
- Unable to take treatment – toxicity/intolerance: 0.3%
- Died in community without seeking care: 0.3%
- Treatment delayed/ineligible for NHS: 0%
- Other: 2.1%
- Not known/not stated: 6.5%

Adapted from Lucas. Clin Med 2008;8:250

Percentage of deaths
Estimated cost of late presentation in Canada – year following diagnosis

Adapted from Krentz et al. HIV Med 2004

N=241 patients, 39% late presenters
Higher cost of medical care for late presenters

Data for 10,433 patients from 7 primary HIV care sites

- Annual total cost of late care is ~2.5 times the cost of care for early therapy (CD4 >500)
- Inpatient costs attributed the most to the total cost in late presenters

Adapted from Gebo KA et al. AIDS 2010
Variation in CD4 count at starting cART

Based on 379,865 pts, LIC (<$1005), LMIC ($1006-$3975), UMIC ($3976-$12,275), HIC (>$12,175)

IeDEA and ARTCC collaboration; JAIDS 2014
Prognosis from starting ART according to pre-therapy CD4 cell counts and HIV-RNA levels

ART Cohort Collaboration, 13 cohort studies from Europe and North America. Analysis of adult patients starting HAART with a combination of at least three drugs (N=12,574)

Mortality and delayed access to care in France

The analysis of data from 18,721 patients was adjusted for sex, age, transmission group, area of enrolment, sub-Saharan African migrant status, enrolment period of time since HIV diagnosis.

Adapted from Lanoy et al. Antiviral Therapy 2007
Onward transmission of HIV (1)

Quinn et al, NEJM 2000

• N=415 serodiscordant couples from 4 US states and Puerto Rico
• 90 HIV seroconversions over 30 mths FU
• none with VL < 1500 cp/ml
Onward transmission of HIV (2)

502 women from Rakai, Uganda, with singleton pregnancies; no transmissions to child when maternal VL < 1000 cp/ml

Maternal ZDV prophylaxis

<table>
<thead>
<tr>
<th>Maternal viral load (geometric mean during pregnancy)</th>
<th>Maternal ZDV prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>N 22</td>
</tr>
<tr>
<td>1000-10,000</td>
<td>83 110 193</td>
</tr>
<tr>
<td>10,000-50,000</td>
<td>75 108 183</td>
</tr>
<tr>
<td>50,000-100,000</td>
<td>16 38 54</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>34 30 64</td>
</tr>
</tbody>
</table>

Adapted from Garcia et al NEJM 1999
Outline

- Definitions and diagnosis of late presentation
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Changes over time in late presentation and CD4 count at HIV-diagnosis: COHERE 2000-2011

N=84,524 HIV+ pts from across Europe

- Late Presentation
- Late presentation with advanced disease
- AIDS
- CD4

Year of diagnosis

7367 7404 8046 7756 8591 8663 8251 8618 9057 7548 3223

Changes in late presentation over calendar time in Southern Europe; stratified by HIV exposure group

Adjusted* odds ratio (95% CI) of late presentation per calendar year later:
Comparison of HIV exposure groups

- MSM: 1.00 (0.97-1.03)
- M Het: 1.03 (0.98-1.07)
- F Het: 1.06 (1.02-1.11)
- M IDU: 1.06 (0.99-1.13)
- F IDU: 0.92 (0.78-1.09)
- Other: 1.05 (0.98-1.11)

N 1095 1029 1559 1901 2212

*Adjusted for age, delayed entry into care (>3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes in late presentation over calendar time in Central Europe; stratified by HIV exposure group

Adjusted* odds ratio (95% CI) of late presentation per calendar year later:
Comparison of HIV exposure groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>0.93 (0.92-0.94)</td>
</tr>
<tr>
<td>M Het</td>
<td>0.97 (0.96-0.99)</td>
</tr>
<tr>
<td>F Het</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td>M IDU</td>
<td>0.99 (0.95-1.03)</td>
</tr>
<tr>
<td>F IDU</td>
<td>0.98 (0.92-1.03)</td>
</tr>
<tr>
<td>Other</td>
<td>0.95 (0.93-0.98)</td>
</tr>
</tbody>
</table>

*Adjusted for age, delayed entry into care (>3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user.
Changes in late presentation over calendar time in Northern Europe; stratified by HIV exposure group

Adjusted* odds ratio (95% CI) of late presentation per calendar year later:
Comparison of HIV exposure groups

- MSM: 0.95 (0.94-0.96)
- M Het: 0.96 (0.95-0.98)
- F Het: 0.97 (0.95-0.98)
- M IDU: 1.01 (0.97-1.04)
- F IDU: 1.00 (0.94-1.07)
- Other: 0.92 (0.91-0.94)


*Adjusted for age, delayed entry into care (>3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user.
Changes in late presentation over calendar time in Eastern Europe; stratified by HIV exposure group

Adjusted* odds ratio (95% CI) of late presentation per calendar year later:
Comparison of HIV exposure groups

- MSM: 1.03 (0.93-1.14)
- M Het: 0.97 (0.86-1.11)
- F Het: 0.89 (0.80-0.98)
- M IDU: 1.11 (0.98-1.25)
- F IDU: 1.12 (0.93-1.34)
- Other: 1.02 (0.83-1.26)

*Adjusted for age, delayed entry into care (>3 months) after HIV diagnosis, region of origin, European region of care, and HIV mode of infection. MSM: males having sex with males. M; male. F; female. Het; heterosexual. IDU; injecting drug user

Changes over time in late presentation and CD4 count at HIV-diagnosis: COHERE 2010-2013

Late presentation with advanced disease
AIDS
Late presentation with very advanced disease
CD4 at diagnosis

N=30,448

Year of diagnosis
2010
2011
2012
2013

N
10765
10054
6259
3370

Mocroft et al, HepHIV 2014
Odds of late presentation per year later testing HIV+

N=30,448

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate*</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Overall</td>
<td>1.01</td>
<td>0.99 – 1.03</td>
<td>0.40</td>
<td>1.00</td>
<td>0.98 – 1.03</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>1.00</td>
<td>0.95 – 1.05</td>
<td>0.95</td>
<td>1.00</td>
<td>0.96 – 1.06</td>
</tr>
<tr>
<td>Central</td>
<td>1.01</td>
<td>0.97 – 1.05</td>
<td>0.64</td>
<td>1.01</td>
<td>0.97 – 1.06</td>
</tr>
<tr>
<td>North</td>
<td>1.01</td>
<td>0.98 – 1.04</td>
<td>0.62</td>
<td>0.98</td>
<td>0.94 – 1.02</td>
</tr>
<tr>
<td>East</td>
<td>1.07</td>
<td>0.91 – 1.25</td>
<td>0.41</td>
<td>1.03</td>
<td>0.88 – 1.21</td>
</tr>
</tbody>
</table>

P=0.073, test for interaction

Late presentation: diagnosed with HIV with a CD4 count below 350/mm$^3$ or an AIDS defining event regardless of the CD4 count, in the 6 months following HIV diagnosis. *Adjusted for age, HIV exposure group, region of origin and age

Mocroft et al, HepHIV 2014
Changes over time in late presentation: HIV exposure group

Percentage LP

Year of diagnosis

N 2010 2011 2012 2013
10765 10054 6259 3370

Adjusted* odds LP per calendar year later testing HIV+

1.18 (1.04 – 1.34)
0.98 (0.92 – 1.04)
1.08 (1.01 – 1.16)
1.00 (0.95 – 1.07)
0.99 (0.96 – 1.02)

P=0.0033, test for interaction

*Adjusted for age, region of care, region of origin and age

Mocroft et al, HepHIV 2014
Reclassification of LP according to clinical stage

Year of HIV diagnosis

% of patients

Cases considered as “LP” by the consensus definition were reclassified as “non-LP” if a recent infection (< 6 months) was reported by clinicians.
Outline

- Definitions and diagnosis of late presentation
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What can do be done to reduce numbers of late presenters?

- One third of the estimated 2.2 million HIV-positive people across the European region are unaware of their HIV status.

- Approximately 50% of those diagnosed are late presenters.

- Client-initiated testing strategies are not sufficient, provider-initiated evidence based testing strategies are needed.

Kutsyna et al, HepHIV Conference, Barcelona 2014
Treatment cascade in United States

Linkage to care: 77% (62%)

MMWR 2011
Treatment cascade in Georgia

Linkage to care: 84% (44%)

Adapted from Chkhartishvili, *HIV Med* 2014
Successful interventions for earlier HIV diagnosis

- Antenatal screening
- Increase in MSM testing
- Screening in GUM clinics
- Screening in TB clinics
- Screening among IDUs
- Indicator condition guided HIV testing
Increased HIV testing correlates with a reduction in late diagnosis of HIV

HIV tests among English STI clinic attendees vs overall UK late HIV diagnosis, 2003–2010

“The proportion diagnosed late (CD4 count <350 cells/mm³) remained high (50%) despite a slow and significant decline over the last decade”

What is indicator condition guided HIV testing?

- An approach using certain conditions, linked with an excess risk of being HIV positive, as indication for health providers to routinely offer an HIV test\(^1-3\)
- Studies suggest that routine HIV testing remains cost-effective, when the undiagnosed HIV prevalence in a specific group, is > 0.1\(^4\)
- The concept of indicator condition guided HIV testing is an approach by which health care practitioners can be encouraged to test more patients based on indicator conditions rather than risk behaviour or group\(^3,4,5\)

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HIDES II Study: Enrolment

- 10139 patients were enrolled; of unknown HIV status and presenting for care with one of the surveyed conditions in one of the clinics.
- Excluded participants: 98 due to missing data; 569 due to age criteria <18 or >65, N=9471 (93.4% of original)
- 42 clinics participated in 20 countries across 4 regions of Europe

Malignant lymphoma of any type; Cervical dysplasia or cancer (cervical CIN II and above), Anal dysplasia or cancer, Hepatitis B viral infection (acute or chronic), Hepatitis C viral infection (acute or chronic), Hepatitis B & C, Ongoing mononucleosis-like illness, Unexplained leukocytopenia and/or thrombocytopenia,(lasting at least 4 weeks), Seborrheic dermatitis/exanthema, Pneumonia, admitted to hospital for at least 24 hours, Unexplained lymphadenopathy, Peripheral neuropathy of unknown cause, Primary lung cancer, Severe or recalcitrant psoriasis, newly diagnosed

Kutsyna et al HepHIV Barcelona 2014
HIV prevalence in the indicator conditions

Overall prevalence: 2.5: 95% CI 2.2 -2.8

Kutsyna et al HepHIV 2014
Targeted, high-quality HIV testing

- Expand alternatives to traditional on-site, clinical HIV antibody testing which use **rapid tests and which provide testing in locations and in conditions that are convenient to clients**

- **Improve links and access to treatment, care and support**, and make the social, legal and policy environment more supportive

- Introduce **provider-initiated testing** and care in prenatal care and in certain other health-care settings

- Use **targeted campaigns to encourage the uptake of HIV testing**

Lazzarus et al, *HIV Med* 2010
Summary

• Late presentation to HIV care (diagnosis and linkage to care) remains common in Europe

• Late presentation has serious implications for the individual patient and for transmission of HIV

• The proportion of late presenters varies across Europe and across risk groups

• Access to HIV testing should be improved

• Provider-driven HIV testing in health care settings (indicator condition guided HIV testing)
Many thanks to those who shared slides

- Jurgen Rockstroh
- Andre Sasse
- Jens Lundgren
- Ole Kirk
- Galyna Kutsyna
Thank you for listening