Rheumatic manifestations of HIV infection

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BHIVA 2009
Plan

• Background
• Review of existing epidemiological studies
• Cross-sectional survey of musculoskeletal pain among HIV positive cohort
• Treatment of rheumatic syndromes

Background

• New York Department of Rheumatology
• 13 patients with seronegative asymmetrical oligoarthritis and enthesitis with at least one of contemporaneous: urethritis, cervicitis, mucocutaneous involvement, oral ulcers, KB
• 9 patients HLA B27 positive
• 5 AIDS, 6 ARC and 2 symptomatic immunodeficiency
• 9/13 arthritis onset synchronous with immunodeficiency

Winchester et al, 1987
Reactive arthritis and HIV

- 12 case reports
- 9 case series
- 4 case-control studies
- 5 cross-sectional surveys
- 3 longitudinal studies
- 1 large retrospective study

**Estimated rates of prevalence: reactive arthritis**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>No of subjects</th>
<th>Country</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>106</td>
<td>Spain</td>
<td>Monteguado, 1991</td>
</tr>
<tr>
<td>0%</td>
<td>140</td>
<td>USA</td>
<td>Simms, 1992</td>
</tr>
<tr>
<td>0.1%</td>
<td>1100</td>
<td>USA</td>
<td>Solinger, 1993</td>
</tr>
<tr>
<td>0.2%</td>
<td>2344</td>
<td>USA</td>
<td>Clark, 1989</td>
</tr>
<tr>
<td>0.5%</td>
<td>1043</td>
<td>USA</td>
<td>Clark, 1989</td>
</tr>
<tr>
<td>0.5%</td>
<td>1133</td>
<td>USA</td>
<td>Hochberg, 1990</td>
</tr>
<tr>
<td>0.5%</td>
<td>556</td>
<td>Spain</td>
<td>Munoz-Fernandez, 1991</td>
</tr>
<tr>
<td>3.8%</td>
<td>52</td>
<td>Canada</td>
<td>Buskila, 1990</td>
</tr>
<tr>
<td>4.6%</td>
<td>65</td>
<td>USA</td>
<td>Winchester, 1988</td>
</tr>
<tr>
<td>8%</td>
<td>74</td>
<td>Mexico</td>
<td>Medina-Rodriguez, 1993</td>
</tr>
<tr>
<td>10%</td>
<td>101</td>
<td>USA</td>
<td>Berman, 1988</td>
</tr>
<tr>
<td>11.2%</td>
<td>89</td>
<td>Argentina</td>
<td>Berman, 1991</td>
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</table>
HIV infection and arthritis: case-control studies

<table>
<thead>
<tr>
<th></th>
<th>Argentina</th>
<th></th>
<th>Mexico</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV +</td>
<td>HIV -</td>
<td>HIV +</td>
<td>HIV -</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26%</td>
<td>2%</td>
<td>45%</td>
<td>2%</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>11%</td>
<td>2%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5%</td>
<td>-</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1%</td>
<td>-</td>
<td>1%</td>
<td>-</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>1%</td>
<td>-</td>
<td>1%</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia/myositis</td>
<td>16%</td>
<td>-</td>
<td>31%</td>
<td>-</td>
</tr>
</tbody>
</table>

Berman, 1991            Medina-Rodriguez, 1993

Rheumatoid arthritis and HIV

- Early reports that rheumatoid arthritis went into remission in association with HIV infection
- BUT: rheumatoid arthritis relapses in patients successfully treated with HAART
- HLA DR4 CD4+ T cells contribute to inflammation in rheumatoid – depleted in active HIV infection
- (comparison with B27 arthropathy = CD8 driven)
African experience

- Reactive arthritis and psoriatic arthritis rare in Africa prior to HIV (HLA B27 low prevalence)
- 17/20 patients with acute arthritis had reactive arthritis, of which 74% HIV+ (none HLA B27+) (Davis 1989)
- Similar findings from Rwanda, Togo, Zambia
- 228/272 spondyloarthritis patients presenting in Zambia were HIV + (84%) (Njobvu, 1998)

Co-existence of HIV and rheumatic diseases

- Case reports and phenomenology
- Very few prospective data
- Rarely controlled data
- Classification often done by HIV physicians or rheumatologists with an ‘interest’, after patients selected and referred – not systematic
- Selection and assignment bias
HAART has changed everything..

- Most available musculoskeletal research pre-HAART
- Phenomenon of ‘immune reconstitution’
- Indinavir and frozen shoulder
- HAART linked to avascular necrosis and perhaps osteoporosis

Brighton cross-sectional survey: Aims

- To quantify the prevalence of musculoskeletal pain among HIV positive men and women
- Understand the impact of musculoskeletal pain in this population
- Explore risk factors for musculoskeletal pain
Cross-sectional survey

- Sampling frame: HIV positive patients attending routine OPD appointments in Brighton, UK (Jan-Oct 2007)
- Validated questionnaire: demographics, musculoskeletal pain, joint swelling & stiffness, skin rashes, inflammatory eye disease and inflammatory bowel disease
- Fracture and risk factors for osteoporosis
- Function, disability, anxiety and depression

1539 HIV positive patients registered 2007
1050 HIV positive subjects attended routine F/Up appointments Jan – Oct 2007
46 Refusals (4%)
145 Non-returned (14%)
859 Responders (82%)
Characteristics of Respondents (n=859)

- 90% male
- Mean age 42 years
- Mean duration of HIV infection 6 years
- Current ARV users 76% (ever users 82%)
- 18% ARV naive
- 40% current cigarette smokers
- 77% current alcohol drinkers

Characteristics of respondents

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=859)</th>
<th>Whole cohort (n=1539)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>90% male</td>
<td>90% male</td>
<td>NSIG</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>42</td>
<td>41</td>
<td>NSIG</td>
</tr>
<tr>
<td>Duration HIV (years)</td>
<td>6</td>
<td>7</td>
<td>NSIG</td>
</tr>
<tr>
<td>ARV naïve (%)</td>
<td>18</td>
<td>24</td>
<td>NSIG</td>
</tr>
<tr>
<td>Stage 1 HIV (%)</td>
<td>57</td>
<td>60</td>
<td>NSIG</td>
</tr>
<tr>
<td>Stage 2 HIV (%)</td>
<td>22</td>
<td>21</td>
<td>NSIG</td>
</tr>
<tr>
<td>Stage 3 HIV (%)</td>
<td>19</td>
<td>17</td>
<td>NSIG</td>
</tr>
</tbody>
</table>
Results: Cross-sectional survey

- 1050 HIV positive eligible to participate
- 859 responders (82%)
- Musculoskeletal Pain lasting > 1 day in past month (n=539, 63%)
- No musculoskeletal pain (320, 37%)
- Musculoskeletal Pain TODAY (n=341, 63%)
- CHRONIC MUSCULOSKELETAL PAIN (>3 months) (n=431, 80%)

Prevalence of pain in the past month by age and gender (n=859)

- % of pain by age and gender:
  - 18-34
  - 35-39
  - 40-44
  - 45-50
  - >50
  - All

- Men (n=775)
- Women (n=84)
Prevalence of pain in the past month by regional site for men and women (n=859)

Prevalence of pain in the past month by regional site among HIV positive women as compared with women aged 45-64 years in North UK
Prevalence of pain in the past month by regional site among HIV positive men as compared with men aged 45-64 years in North UK

Impact of pain
(among 537 reporting pain in past month)

- Mean pain score 5.1 cm
- Mean disability score 4.3 cm
- 188 (35.5%) were taking painkillers most days
- 56 (18%) of those currently employed had taken sick leave because of pain
- 236 (44.9%) had seen their GP about their pain
- 61 (11.5%) had received steroid injections
- 97 (18%) had seen a Rheumatologist
- 65 (12%) had attended A&E with pain
Chronic Musculoskeletal Pain  
(pain lasting > 3 months)

- 447 (82% of those in pain) reported chronic musculoskeletal pain
- Mean duration of pain 4.5 years
- 127 (26 % of those in pain) described chronic widespread pain (pain all over for > 3 months)

Risk factors for pain

Female gender

- Women significantly more likely to report pain (p=0.027)
- Mean pain score higher (p=0.022)
- Women significantly more likely to be taking painkillers most days (p<0.0001)
Risk factors for pain

Age

• Older patients significantly more likely to report
  – pain today (p<0.0001)
  – chronic pain (p=0.004)
• Older patients reported higher prevalence of joint swelling and pain affecting the hip and foot/ankle

HIV-related factors & pain
HAART (n=653)

Current ARV use was significantly associated with

- Pain Last Month
- Pain Today
- Joint Swelling
- Painkillers

* P < 0.05

HAART (n=653)

Current ARV use also significantly associated with

- Knee, Foot/ankle, Hand/wrist pain
- Higher mean disability score (p=0.026)
- Higher mean pain score (p=0.055)
- Higher mean number of painful sites (p < 0.001)
Stage of HIV: symptomatic (stage 2) Versus asymptomatic (n=189)

![Graph showing pain, chronic pain, joint swelling, joint stiffness, arthritis, and painkillers.]

- Pain: *P < 0.05
- Chronic Pain: *P < 0.05
- Joint swelling: *P < 0.05
- Joint stiffness: *P < 0.05
- Arthritis: *P < 0.05
- Painkillers: *P < 0.05

Stage of HIV (n=163)

Compared with those with asymptomatic (Stage 1), Stage 3 (AIDS) was associated with:

- Self-reported diagnosis of arthritis (p=0.003)
- Taking painkillers for musculoskeletal pain most days (p=0.04)
- Foot/ankle pain (p=0.02)
Current markers of viral activity

**Viral load > 40** (n=271)

*protective against*

- Current pain (OR 0.65, p=0.025)
- Joint swelling (OR 0.42, p< 0.001)
- Diagnosis of arthritis (OR 0.44, p=0.002)
- Foot/ankle pain (OR 0.69, p=0.045)

Current markers of viral activity

**CD4 count < 200** (n=59)

*protective against*

- Joint stiffness (OR 0.45, p=0.02)
- Diagnosis of arthritis (OR 0.22, p=0.04)
- Hip pain (OR 0.29, p=0.04)
- Foot/ankle pain (OR 0.50, p 0.08)
Specific ARVs:
Reporting musculoskeletal pain lasting > 1 day in past month (n= 859)

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. taking</th>
<th>No. in pain</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combivir</td>
<td>37</td>
<td>18</td>
<td>0.48</td>
<td>0.24-0.94</td>
</tr>
<tr>
<td>Forsamprenavir</td>
<td>15</td>
<td>14</td>
<td>7.69</td>
<td>1.00-58.83</td>
</tr>
</tbody>
</table>

NOT SIGNIFICANTLY ASSOCIATED:
Efavirenz, Nevirapine, Abacavir, Kivexa, Didanosine, Zalcitabine, Truvada, Lamivudine, Trizivir (n=12), Zidovudine, Tenofovir, Amprenavir, Kaletra, Lopinavir, Ritonavir, Saquinavir, Enfurvitide (n=8), TMC (n=6), IL-2 (n=4)

Risk factors for musculoskeletal pain in the past month (n=859)

<table>
<thead>
<tr>
<th>HIV factors</th>
<th>No (%)</th>
<th>In pain (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current ARVs</td>
<td>657</td>
<td>423 (64)</td>
<td>1.43</td>
<td>1.00-2.04</td>
</tr>
<tr>
<td>Viral load &gt;40</td>
<td>273</td>
<td>166 (61)</td>
<td>0.87</td>
<td>0.64-1.17</td>
</tr>
<tr>
<td>HIV stage 2</td>
<td>190</td>
<td>123 (65)</td>
<td>1.84</td>
<td>1.16-2.91</td>
</tr>
<tr>
<td>HIV stage 3</td>
<td>160</td>
<td>106 (66)</td>
<td>1.42</td>
<td>0.89-2.27</td>
</tr>
<tr>
<td>Hep B +ve</td>
<td>16</td>
<td>11 (69)</td>
<td>1.93</td>
<td>1.06-3.50</td>
</tr>
<tr>
<td>Hep C +ve</td>
<td>11</td>
<td>6 (55)</td>
<td>0.71</td>
<td>0.22-2.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>No (%)</th>
<th>In pain (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess</td>
<td>79</td>
<td>39 (49)</td>
<td>0.53</td>
<td>0.32-0.88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mental Health</th>
<th>No (%)</th>
<th>In pain (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>254</td>
<td>155 (61)</td>
<td>1.64</td>
<td>1.20-2.30</td>
</tr>
<tr>
<td>Poor</td>
<td>256</td>
<td>203 (79)</td>
<td>4.00</td>
<td>2.70-5.90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitality</th>
<th>No (%)</th>
<th>In pain (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>281</td>
<td>185 (66)</td>
<td>2.11</td>
<td>1.5-3.0</td>
</tr>
<tr>
<td>Poor</td>
<td>222</td>
<td>173 (78)</td>
<td>3.86</td>
<td>2.60-5.75</td>
</tr>
</tbody>
</table>

NB Smoking, BMI not associated
Summary

• High frequency and severity of pain in HIV + patients compared to non-HIV studies
• HIV positive women reported higher prevalence of pain and higher mean pain and disability scores
• Univariate risk factors similar to non-HIV studies: age, gender, psychological wellbeing
• Symptomatic stage of HIV & current usage of ARVs associated with pain and joint symptoms

Treatment of rheumatic disease in HIV

• Rheumatologists can help.
• Pain management approach
• Diet and lifestyle advice
• Exercises
• Occupational therapy / Physiotherapy / Podiatry / orthoses and appliances
• Topical therapies, analgesics, NSAIDs, COX-2 inhibitors, amitryptilene
Intra-articular and intra-muscular steroid injections

- 35 patients – 29 male; 6 female
- 31 HAART
- 26 intra-articular and 9 intra-muscular steroid injections
- Mean pain score prior to injection 8.3cm and mean score post-injection 2.9cm
- No significant change in CD4 count or viral load and NO complications

Glennon K, Walker-Bone K BSR AGM 2009

Immunosuppressive treatment of rheumatic disease in HIV

- COMPLEX because of co-existent immunosuppression
- Rule of thumb: CD4 count > 200 and viral load undetectable then can safely use immunosuppression
- DIFFICULT when compromised: simple first (steroids; sulphasalazine; hydroxychloroquine)
- Used MMF twice now safely
- MTX: ? Safe to use
- Anti-TNF: used in a small number of patients
Conclusion

• HIV infection is associated with musculoskeletal pain among >60% of patients
• Active HIV infection precipitates inflammatory syndromes and HAART is associated with immune reconstitution syndromes
• Women may be more ‘at risk’ than men
• Psychological wellbeing is an important factor
• HIV-associated factors also play a role
• A multidisciplinary approach with Rheumatology can be very effective

Acknowledgements

Dr Edwina Lawson
Ms Katie Glennon
Dr Martin Fisher
Dr Duncan Churchill
Dr Yvonne Gilleece
Dr Daniel Richardson
Dr Gillian Dean
Dr Charlotte Bell
Dr David Pao
Dr Kate Nambiar
Dr Charlotte Short
Ms Nicky Perry

NHS R&D
15th Annual Conference of the British HIV Association (BHIVA)

1-3 April 2009, Arena and Convention Centre Liverpool