

15TH ANNUAL CONFERENCE OF THE
BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association
BHIVA

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Brighton and Sussex NHS
University Hospitals

Brighton and Sussex
medical school

**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

Prevalence	No of subjects	Country	Author
0%	106	Spain	Monteguado, 1991
0%	140	USA	Simms, 1992
0.1%	1100	USA	Solinger, 1993
0.2%	2344	USA	Clark, 1989
0.5%	1043	USA	Clark, 1989
0.5%	1133	USA	Hochberg, 1990
0.5%	556	Spain	Munoz-Fernandez, 1991
3.8%	52	Canada	Buskila, 1990
4.6%	65	USA	Winchester, 1988
8%	74	Mexico	Medina-Rodriguez, 1993
10%	101	USA	Berman, 1988
11.2%	89	Argentina	Berman, 1991

HIV infection and arthritis: case-control studies

	Argentina		Mexico	
	HIV +	HIV -	HIV +	HIV -
Arthralgia	26%	2%	45%	2%
Reactive arthritis	11%	2%	8%	0%
Arthritis	5%	-	10%	-
Psoriatic arthritis	1%	-	1%	-
Septic arthritis	1%	-	1%	-
Myalgia/myositis	16%	-	31%	-

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*)
- Increasing prevalence of psoriatic arthritis in 2000 in Zambia (27/28 patients HIV +) (*Njobvu, 2000*)

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

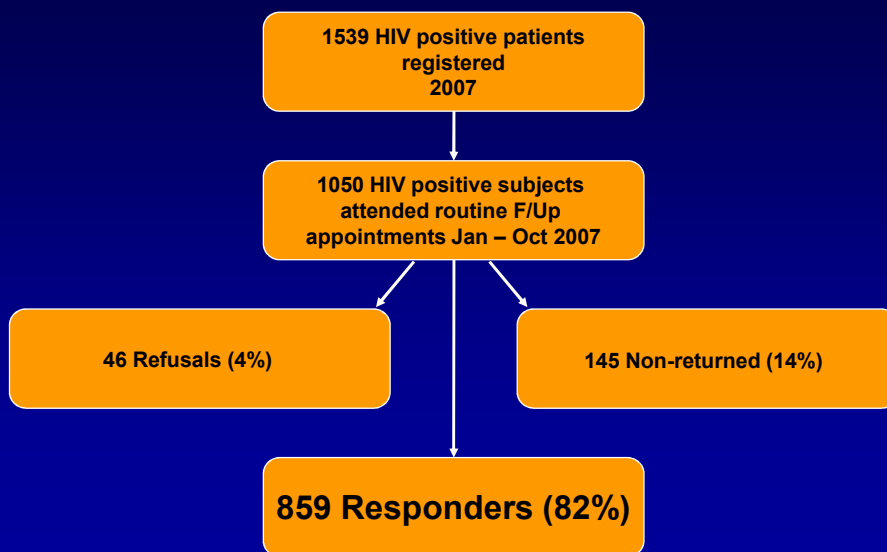
Brighton cross-sectional survey: Aims

- 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

Cross-sectional survey



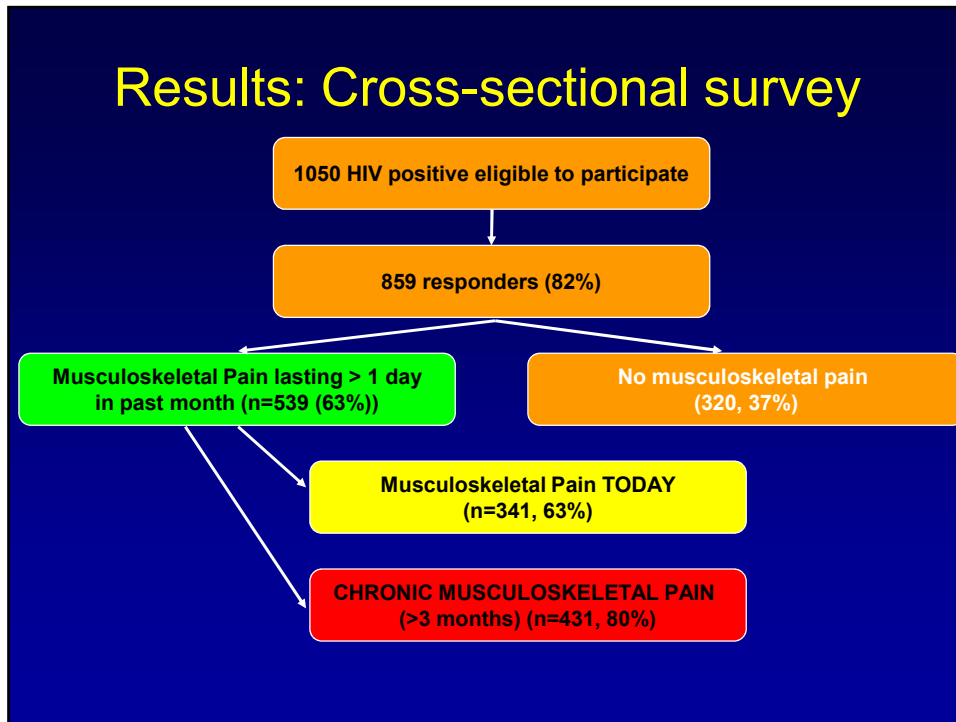
Characteristics of Respondents (n=859)

- 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

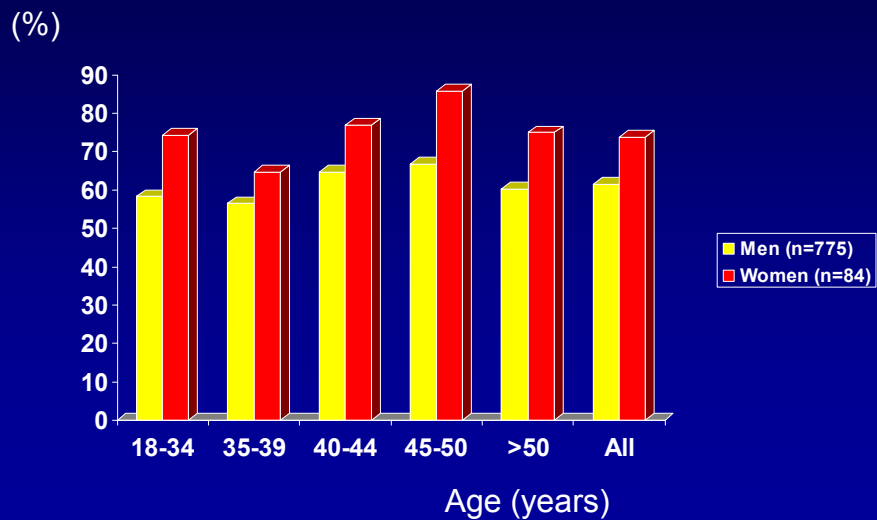
Characteristics of respondents

	Responders (n=859)	Whole cohort (n=1539)	P-value
Gender	90% male	90% male	NSIG
Median age (years)	42	41	NSIG
Duration HIV (years)	6	7	NSIG
ARV naïve (%)	18	24	NSIG
Stage 1 HIV (%)	57	60	NSIG
Stage 2 HIV (%)	22	21	NSIG
Stage 3 HIV (%)	19	17	NSIG

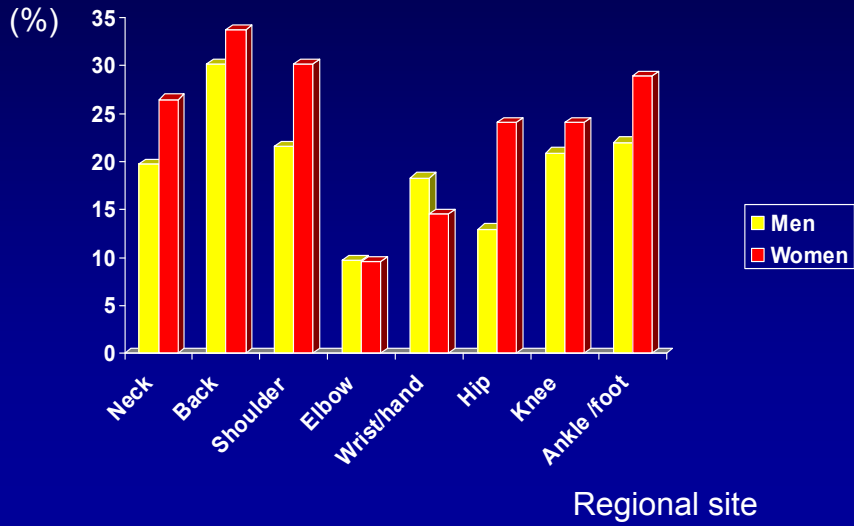
Results: Cross-sectional survey



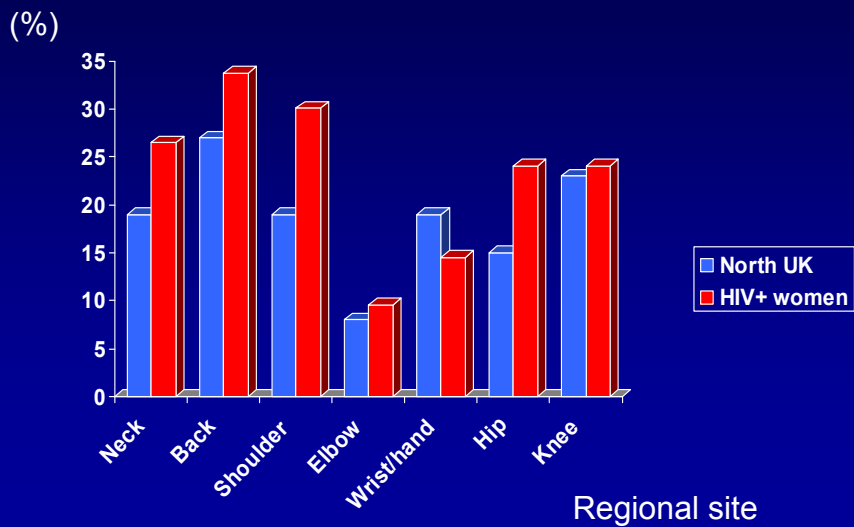
Prevalence of pain in the past month by age and gender (n=859)



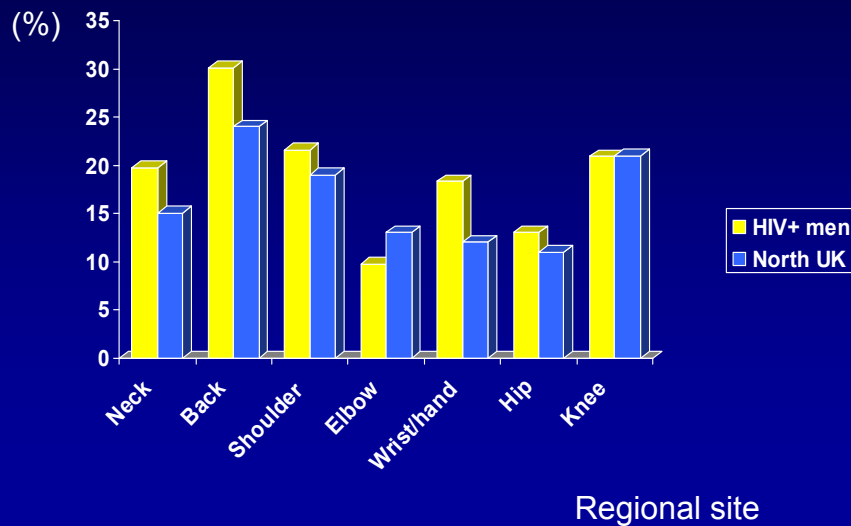
Prevalence of pain in the past month by regional site for men and women (n=859)



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 **5.1cm**
- 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

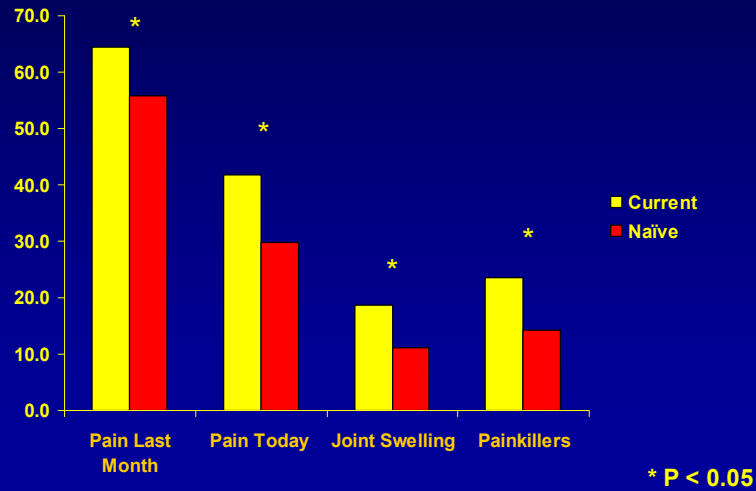
Age

- 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

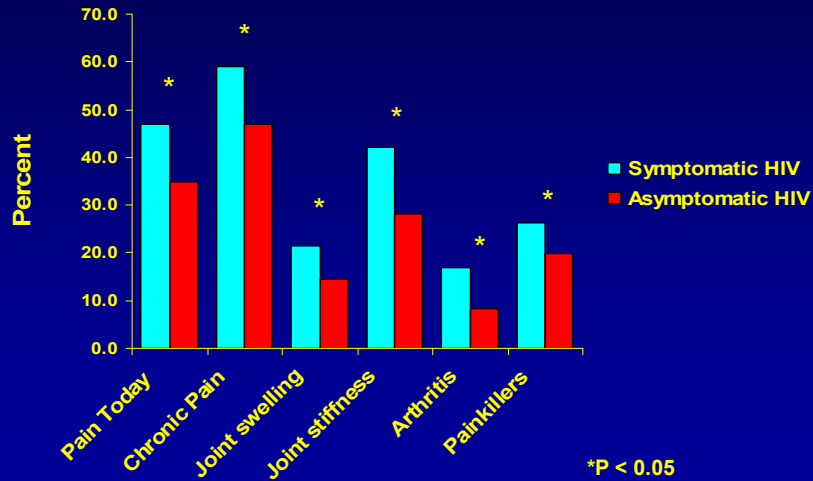


HAART (n=653)

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)



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)

Drug	No. taking	No. in pain	OR	95% CI
Combivir	37	18	0.48	0.24-0.94
Forsamprenavir	15	14	7.69	1.00-58.83

NOT SIGNIFICANTLY ASSOCIATED:

Efavirenz, Nevirapine, Abacavir, Kivexa, Didanosine, Zalcitabine, Truvada, Lamivudine, Trizivir (n=12), Zidovudine, Tenofovir, Amprenavir, Kaletra, Lopinavir, Ritonavir, Saquinavir, Enfuvirtide (n=8), TMC (n=6), IL-2 (n=4)

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

		No (%)	In pain (%)	Odds ratio	95% CI
HIV factors	Current ARVs	657	423 (64)	1.43	1.00-2.04
	Viral load >40	273	166 (61)	0.87	0.64-1.17
	HIV stage 2	190	123 (65)	1.84	1.16-2.91
	HIV stage 3	160	106 (66)	1.42	0.89-2.27
	Hep B +ve	16	11 (69)	1.93	1.06-3.50
	Hep C +ve	11	6 (55)	0.71	0.22-2.34
Alcohol	Excess	79	39 (49)	0.53	0.32-0.88
Mental Health	Moderate	254	155 (61)	1.64	1.20-2.30
	Poor	256	203 (79)	4.00	2.70-5.90
Vitality	Moderate	281	185 (66)	2.11	1.5-3.0
	Poor	222	173 (78)	3.86	2.60-5.75

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, amitriptylene

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

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NHS R&D



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