

## SHORT REPORT

# Biological treatment usage in patients with HIV and rheumatic disease, 2003–2021: long-term safety and follow-up

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**ABSTRACT**

**Objective** This study examined the safety and efficacy of biological agents, especially tumour necrosis factor (TNF) inhibitors, for HIV-positive rheumatology patients refractory to standard therapy.

**Methods** This study is a retrospective case series including patients derived from a community HIV clinic as well as from two academic centres. Initial visit data collected included: sociodemographic characteristics, CD4 counts, HIV viral load and medication use. Patients with persistent disease activity despite standard conservative therapy were begun on biological agents. The main outcomes were patient and physician global assessment of treatment response and medication side effects in patients with rheumatological disorders treated with biological medications over time.

**Results** Seventeen patients were seen from 2003 to 2021, including eight from our previous cohort published in 2008 and nine seen since then, five of whom taking TNF blockers for more than 10 years. Three (17.7%) had rheumatoid arthritis, five (29.4%) psoriatic arthritis, four (23.5%) axial spondyloarthritis and the rest (29.4%) peripheral spondyloarthritis. Antiretroviral therapy had been used in 15. All but one had at least a partial response to biological therapy. There were no major infectious episodes necessitating the discontinuation of medications with only one patient discontinuing treatment due to rising HIV viral load. Patients not on antiretroviral therapy reported no adverse side effects from biological therapy. Four patients were switched to ustekinumab, secukinumab, tocilizumab or upadacitinib from anti-TNF therapy without complications.

**Conclusions** These data suggest that biological therapy, especially anti-TNF agents are safe and well tolerated in HIV positive individuals even over several years.

**INTRODUCTION**

Tumour necrosis factor (TNF)- $\alpha$  plays an essential role in the host defence against intracellular pathogens; however, TNF- $\alpha$  has also been implicated in the pathogenesis of HIV-1 infection by promoting HIV replication in T-cell lines and in lymphocytes.<sup>1–3</sup> Anti-TNF therapy and other biological treatments are now commonly used in patients

**KEY MESSAGES**

- ⇒ Studies reporting anti-tumour necrosis factor (TNF) and other biological usage in patients with HIV infection have mostly been at the case-report level.
- ⇒ We previously reported in 2008 our experience with the use of anti-TNF agents in patients with HIV infection, the largest case series reported to date.
- ⇒ We here report the long-term follow-up data on these eight patients as well as on an additional nine patients we have seen since our original report.
- ⇒ These data show that anti-TNF agents are safe, effective and well tolerated in patients with HIV infection, even after over 15 years of follow-up as well as standard guidelines are followed.
- ⇒ Other biologics, including IL-6 and IL-17 inhibitors, as well as Janus kinase inhibitors were well tolerated in individual patients.

suffering from rheumatological conditions; however, their usage in HIV-1 patients has been met with concern given that anti-TNF therapy increases susceptibility to infections especially with *Mycobacterium tuberculosis*, atypical mycobacteria and as well as other microorganisms.<sup>4</sup> Little is known regarding the safety and efficacy of newer biologics developed over the last decade, such as interleukin-6 (IL-6), interleukin 12/23 (IL-12/23), interleukin-17 (IL-17) and Janus kinase (JAK) inhibitors. However, there have been such studies reported in patients with HIV infection and psoriasis.<sup>5</sup>

We previously reported our experience with anti-TNF agent usage in eight HIV positive patients with rheumatic diseases in 2008.<sup>6</sup> Few case reports published since that time have reported long-term follow-up data. Given that patients with rheumatic conditions in the setting of HIV-1 infection may not respond to conventional therapy, we sought to analyse the efficacy of treatment for various rheumatic conditions treated with anti-TNF therapy as well as other biological agents.



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Additionally, we assessed the safety of biologics through documentation of adverse side effects through the course of every patient's care on anti-TNF therapy or other biological treatment. Thus, the primary outcomes of our study are the safety and efficacy of these medications for patients with concomitant HIV infection and rheumatic disease followed over the course of their care.

## METHODS

This cohort includes 15 patients seen at Thomas Street Clinic, the HIV outpatient clinic operated by the Harris County Hospital District since 1989 (of whom two patients subsequently transferred their care to the University of Texas McGovern Medical School University Practice (UT-H)) as well as two other patients seen over the same period in whom the senior author (JDR) was either directly (at UT-H) or indirectly (with the primary rheumatologist at the Cedars-Sinai Medical Centre (MI)) involved in their care, both included in our original series.<sup>6</sup> All patients had rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA). All but one of the patients were cared for by the senior author (JDR) who confirmed the diagnoses by clinical impression as well as by approved criteria and that the inclusion and exclusion criteria were met.<sup>7–10</sup> The remaining patient, seen at Cedars-Sinai Medical Centre and reported previously,<sup>6</sup> had the diagnosis confirmed by the site rheumatologist (MI). In this study, not only do we present long-term follow-up data on the original eight patients, but include nine additional patients that we have cared for since then in whom biological treatment was used in the setting of HIV infection, including four patients that switched from anti-TNF therapy to other biological agents such as IL-6, IL-12/23, IL-17 and JAK inhibitors with no significant side effects. At baseline and subsequent visits, the following were collected: patient demographics, associated rheumatic disease, the presence and type of combined antiretroviral therapy (cART) used as well as other medication use, CD4 counts and viral loads. In addition to chart review, the investigators used the US Social Security Death databases to find patients that were lost to follow-up. All patients were screened for latent tuberculosis at their first clinic visit with those on biological therapy rechecked annually. Additionally, patients were also screened for hepatitis A, B and C at their first clinic visit with liver function tests monitored at least annually. If the patient had hepatitis C, they were treated with anti-HCV medications. We defined efficacy with the remission of symptoms by patient and physician global assessments. Moreover, we defined safety in this study as the lack of adverse side effects such as infection or allergic reaction, specifically, by serious infection as requiring hospitalisation or the need for drug discontinuation as a direct result, allergic response of other serious side effect. Disease activity scores, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) levels were not consistently collected at every visit. Moreover,

ESR and CRP are more difficult to interpret in the setting of HIV infection. Follow-up visits were scheduled every 4–6 months, often depending on other medications that were being taken or as their disease required. Inclusion criteria were that the patient had concomitant HIV-1 infection and a rheumatic disease where anti-TNF therapy was commonly used, specifically RA, SpA or PsA, where the patient had active disease as judged by the clinician refractory to non-steroidal anti-inflammatory drugs and/or disease-modifying antirheumatic drugs (DMARDs). Exclusion criteria included patients that were on anti-TNF therapy not long enough to evaluate efficacy. With the recommendations for immunosuppressive agents in HIV-1 positive patients, anti-TNF therapy was not started in any individual with a CD4 count of less than 200 cells/ $\mu$ L or a HIV-1 viral load of greater than 60 000 copies/ $\text{mm}^3$ .<sup>11</sup> Laboratory studies were performed through the commercial laboratories usually used by these clinics. The decision to change biological, therapy was made based on either lack of response or drug side effects, just as would be done in the non-HIV setting. For this study, descriptive statistical analyses were performed.

## RESULTS

Between February 1994 and February 2022, 1797 unduplicated patients were seen at the Thomas Street Clinic, of whom 20 had RA, 22 PsA and 60 SpA, including 3 with ankylosing spondylitis (AS), 2 with non-radiographic axial SpA and 55 with either peripheral or undifferentiated SpA (non-AS patients seen before the axial and peripheral SpA criteria were published<sup>8,9</sup> were called undifferentiated SpA). Of these, 15 were treated with anti-TNF or other biological/anti-JAK agents (2 RA-10%, 4 PsA-18.2%, 4 Axial SpA/AS-80% and 5 peripheral/undifferentiated SpA-9.1%). Including the additional two patients described above, 17 patients with rheumatic diseases refractory to DMARDs were treated with anti-TNF or other biological agents seen between 2003 and 2021. The current status of the original eight patients published in 2008 are shown in [table 1](#), and the data on the additional nine patients included since then in [table 2](#). Three patients were lost to follow-up, two in 2015, and one in 2018 with duration of long-term follow-up of 12, 14 and 9 years, respectively. The average age at first visit was  $42.9 \pm 7.8$  years and 64.7% were male. In addition, our cohort was predominantly black (70.6%) with three white (17.7%) and two Latino patients (11.8%) respectively. Baseline CD4 count was  $765.5 \pm 570.9$  cells/ $\mu$ L with the lowest CD4 count on biological therapy was  $641.8 \pm 344.5$  cells/ $\mu$ L and the most recent average CD4 count  $1013.7 \pm 922.4$  cells/ $\mu$ L. No patient in our cohort dropped below 200 cells/ $\mu$ L with cART being used in 82.4%. There were no infectious episodes requiring hospitalisation that necessitated the discontinuation of medications while on biological therapy. From our cohort of 17 patients, 4 (23.5%) switched from anti-TNF to other biological or JAK inhibitor treatment. Patients who were

**Table 1** HIV-1 positive patients seen from 2003 to 2007 on anti-TNF therapy

Patient number	1	2	3	4	5	6	7	8
Age at first visit	48	34	31	49	44	39	47	52
Gender	Male	Male	Male	Female	Female	Male	Female	Male
Ethnicity	White	White	Black	Black	Black	Black	Black	White
Rheumatic disease	Seropositive RA plus psoriasis	ankylosing spondylitis (AS)	Peripheral SpA	Peripheral SpA	Seronegative RA	PsA	PsA	PsA
Biologic/JAK inhibitor usage	Currently taking	Taken previously	Not taking	Switched to tocilizumab	Not taking	Not taking	Switched to secukinumab then ustekinumab	Lost to follow-up
Taking cART	Yes	Yes	No	Yes	No	No	Yes	Yes
Baseline CD4 (cells/ $\mu$ L)	631	634	745	373	1300	970	365	268
Baseline viral load (copies/mL)	Undetectable	256	Undetectable	Undetectable	Undetectable	27 829	15 667	Undetectable
Duration of anti-TNF treatment	2003–2011, 2016–present	2004	2003–2005	2003–2017	2004–2005	2004–2007	2006–present	2003–2007
Still followed	Current patient	Followed elsewhere after 2006, alive 2021	Last visit 2015	Current patient	Current patient	Last visit 2018	Current patient	Last seen 2015
Lowest CD4 on anti-TNF treatment (cells/ $\mu$ L)	357	634	923	580	1082	750	382	240
Highest viral load on anti-TNF treatment (copies/mL)	103	845	Undetectable	120 000	Undetectable	428 503	<400	Undetectable
Most recent CD4 count (cells/ $\mu$ L)	468	690	535	1026	993	321	1121	417
Most recent HIV viral load (copies/mL)	Undetectable	Undetectable	193	Undetectable	Undetectable	77	Undetectable	Undetectable
Anti-TNF agent used	Etanercept, Adalimumab	Etanercept	Etanercept	Etanercept, adalimumab, infliximab	Etanercept	Etanercept, infliximab, adalimumab	Etanercept, adalimumab, infliximab	Etanercept, infliximab

Continued

**Table 1** Continued

	None	None	None	none	Secukinumab, ustekinumab	None
Other biologic/anti-JAK agents used	None	None	Tocilizumab	none	Secukinumab, ustekinumab	None
Clinical response to therapy	Excellent	Transient	Partial	Excellent	Etanercept-transient infliximab-excellent, adalimumab-partial	Etanercept- no response, infliximab- excellent
Complications of biological treatment	Psoriasis (etanercept)	None	None	None	Etanercept allergy, Golimumab shingles, Secukinumab allergy	Facial abscess (infliximab)
cART, combined antiretroviral therapy; JAK, Janus kinase; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; TNF, tumour necrosis factor.						

not on cART reported no adverse side effects to biological therapy and no opportunistic infections. Moreover, for patients that were taking daily corticosteroids, there were no complications with biological treatment. In the overall cohort, three (17.7%) had RA, five (29.4%) PsA, three (17.7%) axial SpA and the rest (35.5%) peripheral SpA, including three previously classified as reactive arthritis. From our cohort, 12 patients had a good to excellent clinical response to biological therapy with near total symptomatic remission (by physician and patient assessment). Additionally, four patients had a partial or transient response with only one patient having no perceived benefit from anti-TNF therapy. Eleven patients had no adverse side effects of biological therapy. Patient 1 in our series experienced one herpetic lesion 1 week after beginning etanercept; however, there was a previous history of recurrent herpetic lesions and his symptoms resolved without any treatment or complications. In addition, patient 1 had a history of recurrent facial abscesses secondary to poor dentition both on and off biologic and he was subsequently taken off this treatment in 2021 in anticipation of dental implant surgery. Patient 3 was the only one in our cohort that developed anterior acute uveitis while on etanercept therapy. Patients 6 and 9 had transient increases in HIV-1 viral load requiring temporary discontinuation, but this did not recur with subsequent treatments. Patient 8 had a facial abscess while on infliximab that responded to antibiotic therapy that resolved without any further complications or recurrence. Furthermore, patient 7 had an allergy to secukinumab as was switched to ustekinumab. Three patients switched from anti-TNF therapy to interleukin inhibitors due to disease flares on treatment and had symptom remission thereon. Patient 13 switched from etanercept to upadacitinib due to persisting symptoms and has had an excellent clinical response to treatment.

**DISCUSSION**

This retrospective case series builds on and extends our previous report that suggests the use of biological agents is safe and effective in HIV-1 positive patients with rheumatic diseases, now even long term. Biological agents were begun only when patients failed initial standard antirheumatic therapy and treatment was not started unless CD4 count was >200 mm<sup>3</sup> and HIV viral load was <60 000 copies/mm<sup>3</sup>.<sup>11</sup> There were no infectious events that necessitated permanent discontinuation of therapy; however, given that there was no HIV-1 positive control group, it is impossible to speculate the significance of this. However, there has been research that has shown that HIV-infected patients on anti-TNF therapy have the same rate of serious infection as patients from registries.<sup>12</sup>

Since our publication in 2008, there have been a few case reports that address anti-TNF treatment and other biological therapy with HIV-1 infection: one using etanercept, one using infliximab, and one using

**Table 2** HIV-1 positive patients seen from 2008 to 2021 on anti-TNF therapy

Patient number	9	10	11	12	13	14	15	16	17
Age at first visit	35	30	49	36	48	49	36	53	49
Gender	Male	Male	Female	Male	Black	Male	Male	Female	Female
Ethnicity	Black	Hispanic	Black	Black	Black	Black	Hispanic	Black	Black
Rheumatic disease	Enteropathic arthritis (Peripheral SpA)	PsA	Ankylosing spondylitis (AS)	PsA	Seronegative RA	Non-radiographic axial SpA	Peripheral SpA	Non-radiographic axial SpA	Peripheral SpA
Anti-TNF agent usage	Not taking	Currently taking	Not taking	Currently taking	Switched to upadacitinib	Not taking	Currently taking	Switched to secukinumab	Currently taking
Taking cART	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baseline CD4 (cells/ $\mu$ L)	583	185	614	562	599	440	1300	827	2618
Baseline viral (copies/mL)	1788	535	Undetectable	4500	384	Undetectable	Undetectable	Undetectable	Undetectable
Duration of anti-TNF treatment	2006–2010	2010–present	2013–2013	2010–present	2013–2016, 2020–present	2014–2014	2019–present	2020–present	2020–present
Still followed	Last seen 2015	Current patient	Current patient	Current patient	Current patient	Current patient	Current patient	Current patient	Current patient
Lowest CD4 on anti-TNF treatment (cells/ $\mu$ L)	403	303	677	217	599	389	1144	815	1416
Highest viral load on anti-TNF treatment (copies/mL)	35200	43700	Undetectable	45500	384	Undetectable	Undetectable	8390	Undetectable
Most recent CD4 count (cells/ $\mu$ L)	583	771	1040	365	266	592	1757	3886	2402
Most recent HIV viral load	164000	38	Undetectable	14000	Undetectable	Undetectable	Undetectable	Undetectable	Undetectable
Anti-TNF agent used	Adalimumab	Etanercept, adalimumab	Etanercept	Adalimumab, etanercept	Etanercept	Etanercept	Adalimumab	Adalimumab	Adalimumab
Other biologic/anti-JAK agents used	None	None	None	None	Upadacitinib	None	None	Secukinumab	None
Clinical response to therapy	Partial	Etanercept-transient, adalimumab-good	Good	Adalimumab-transient, etanercept-good	Excellent	Transient	Excellent	Good	Good
Complications of biological treatment	Rising viral load	None	None	None	None	None	None	None	None
cART, combined antiretroviral therapy; JAK, Janus kinase; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; TNF, tumour necrosis factor.									

secukinumab.<sup>13–15</sup> Liang *et al* described one patient on etanercept for RA long-term which demonstrated safety and efficacy; while, Rafael *et al* described a patient that was successfully treated with infliximab for Crohn's disease. Vilchez-Oya *et al* described one case of secukinumab for axial SpA and reviewed four additional cases of anti-IL-17 monoclonal antibody use that demonstrated safety and efficacy in this setting. Also, as previously noted, was a series of 23 patients with HIV infection with psoriasis, but without rheumatic disease, treated with etanercept, methotrexate or ustekinumab.<sup>5</sup> However, our study adds to and further elaborates on these case studies by reporting on 17 patients followed between a period of 2–18 years with a variety of rheumatic conditions on anti-TNF and other biological therapy. Not only have our patients demonstrated long-term safety in the use of these therapeutic agents; but they have had long-term effectiveness and symptom remission while on therapy through clinician and patient assessment.

Strengths of this study include granular long-term follow-up data on a cohort of patients with concomitant HIV-1 infection and clinician-diagnosed rheumatic disease. A weakness includes the lack of quantitative measures that could have been used to document the efficacy of these therapies. However, any adverse side effect was documented in the medical record as well as any cause for hospitalisation. Thus, over long-term follow-up, anti-TNF and IL-blocking agents appear to be safe and efficacious in patients with HIV-1 with concomitant rheumatic conditions. For patients that have failed standard rheumatic therapy, these agents provide a means for achieving symptomatic remission without major adverse opportunistic infections or any detrimental effects on CD4 counts or viral load. These data underscore that if a patient's HIV-1 infection is well controlled and the patient not significantly immunocompromised, biological agents can be considered as a viable option for treating a variety of rheumatic diseases.

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**Collaborators** not applicable.

**Contributors** BSN did the data abstraction from the charts and wrote this manuscript, and presented the data at the 2021 American College of Rheumatology Convergence meeting. GS and FMW assisted in the care of these patients at Thomas Street Clinic over the years, and MI provided the clinical data from the one Cedars-Sinai patient in this and the 2008 manuscript. JDR supervised the care of these patients since the inception of the clinic in 1990. All these authors assisted in the drafting and final approval of this article.

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**Competing interests** None declared.

**Patient and public involvement statement** The risks and benefits of biological therapy in the setting of HIV infection were discussed with all of the patients whose deidentified clinical data were presented in this and our previous manuscript, as well as that sharing these experiences would likely result in the better care of patients with HIV presenting with rheumatic diseases and all patients approved.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the University of Texas Medical School Committee for the Protection of Human Subjects (HSC-MS-09-0672).

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