

1 Systematic review of the efficacy and safety of biological therapy for  
2 inflammatory conditions in HIV-infected individuals

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34 **Introduction**

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36 Biologic therapies are a class of protein drugs that target specific chemicals or  
37 cells in the human immune system. Most licensed biologic agents antagonise  
38 cytokines to treat a range of immune-mediated inflammatory diseases (Table 1).  
39 More than 90% of biologic therapies used for inflammatory conditions target  
40 tumour necrosis factor-*alpha* (TNF-*a*) (1). Like other biologic therapy targets,  
41 TNF-*a* has protean pro-inflammatory effects *in vivo*, such as inflammatory cell  
42 recruitment and release of additional cytokines interleukin-1 (IL-1) and IL-6 (2).  
43 Multiple therapeutic mechanisms have been employed to down-regulate its  
44 effects, including monoclonal antibodies that target TNF-*a* directly (e.g.  
45 infliximab), and neutralising soluble receptor antagonists (e.g. etanercept).  
46 These therapies have transformed care for HIV-negative populations with severe  
47 inflammatory conditions. Approximately 70% of anti-TNF-*a* agents used globally  
48 are prescribed for rheumatoid arthritis (3). In the UK approximately 6% of  
49 patients with rheumatoid arthritis (RA), over 12,000 individuals, receive biologic  
50 [drugs](#). This is closer to 12% in The Netherlands and Spain where clinical  
51 thresholds for biologic therapy are lower (3).

52

53 While such agents dampen inflammation, they may also impair appropriate  
54 immune responses to infection, although the precise mechanisms are poorly  
55 understood (4,5). In light of this potential increased infection risk, HIV-infected  
56 individuals have not been included in randomised controlled trials of biologic  
57 therapies alongside elderly and other co-morbid patients that are thought to  
58 constitute nearly one third of current real-life biologic therapy use (6). Clinical  
59 data reporting use of biologic therapy for inflammatory disease in HIV-infected  
60 individuals are largely limited to case reports and case series. Literature reviews  
61 are limited to single specialty journals and do not cover the full spectrum of  
62 inflammatory conditions that affect HIV-infected individuals. There is a more  
63 substantial literature on use of biologic agents as chemotherapy for  
64 haematological malignancy in HIV-infected individuals (7).

65

66 In this article we review published data on the use of biologic therapies used to  
67 treat inflammatory conditions in HIV-infected individuals, focusing on, but not  
68 limiting discussion to, dermatological, gastroenterological and rheumatological  
69 indications. The paper also considers the clinical need for biologic therapy in the  
70 treatment of immune-mediated pathology in HIV-infected individuals. We  
71 address what might be extrapolated regarding efficacy and safety data from the  
72 biologic therapies literature of HIV-associated malignancy and HIV-uninfected  
73 populations.

74

## 75 **Methods**

76

77 The primary purpose of this systematic review was to provide an overview of all  
78 available studies of biologic treatments of non-malignant and non-  
79 lymphoproliferative inflammatory conditions in HIV-positive patients. The  
80 review focuses on dermatological, gastrointestinal, and rheumatological  
81 indications for biologic therapy. The range of biologic treatments examined was  
82 limited to those medications recommended by the National Institute for Health  
83 and Care Excellence (NICE) up to 1 July 2015, to pragmatically capture those  
84 therapies in current use. Since that date anakinra has been removed from RA  
85 treatment guidelines however the agent was included in our literature search.  
86 The study conduct was in accordance with the PRISMA statement for systematic  
87 reviews.

88

89 Search strategy:

90 Studies were extracted from search of online databases Embase and Medline  
91 (OvidSP) up to 1 July 2015. The search was restricted to adult articles from the  
92 English literature (Figure 1; [Supplementary Material: Additional file 1: Search](#)  
93 [Strategy](#)).

94

95 Initial screening of the titles and abstracts excluded animal studies, basic science  
96 studies, duplicate publications, and identified studies primarily on biologic  
97 therapy for inflammatory disease in HIV-infected individuals. The full texts of the  
98 remaining 52 articles were assessed by two authors for eligibility. Thirty-seven

99 papers were collected for final review. All English language case reports, case  
100 series and both prospective and retrospective observational studies were  
101 included. References, guidelines and expert opinion were consulted for  
102 additional information.

103

## 104 | **Results**

105

106 Clinical need is poorly defined in HIV-infected individuals. Prevalence data on  
107 inflammatory conditions in HIV-infected populations are based largely on case  
108 reports, case series and single-centre studies. These heterogeneous data are  
109 further limited by the variable application of standardised disease classifications  
110 (8). This may be due to the absence of specific diagnostic tests or the lack of  
111 collaboration with specialty physicians (9). The natural history of inflammatory  
112 diseases in HIV-infected individuals is also complex. Onset of inflammatory  
113 pathology may be HIV-associated or independent of HIV infection, either  
114 preceding or postdating HIV acquisition. Case reports describe occult  
115 inflammatory disease unmasked both by HIV-mediated immunosuppression  
116 (10) and paradoxically after restitution of the immune system by initiation of  
117 antiretroviral therapy (ART) (11,12). Inflammatory manifestations associated  
118 with, or intrinsic to, HIV infection are well recognised and may mimic recognised  
119 conditions, in particular rheumatologic manifestations (13). Describing the  
120 confounding effect of HIV infection and ART on any of these processes is  
121 complicated and there are no comprehensive long-term prospective data (9).  
122 Despite this paucity of information inflammatory conditions are considered  
123 common in HIV-infected individuals with possibly different disease courses  
124 compared with HIV-uninfected populations.

### 125 Specific inflammatory conditions in HIV-infected individuals

126 Rheumatologic symptoms are common in HIV-infected individuals. In a large  
127 retrospective analysis of North American inpatients, arthritis or arthralgia was  
128 reported in 5.5% of HIV-infected individuals (13). High positive rates of non-  
129 specific autoantibodies, such as antinuclear antibodies (ANA) and rheumatoid  
130 factor (RF), were described in HIV-infected individuals in studies prior to ART

131 (14), however seroprevalence after initiating modern ART regimens are thought  
132 to be comparable to rates in the general population (15). Pre-ART era data  
133 suggested that rheumatoid arthritis and HIV-infection were mutually exclusive:  
134 the decline in CD4+ T cells mitigating lymphocyte-mediated autoimmunity (16).  
135 This dogma may have significantly prejudiced the nomenclature of subsequent  
136 studies. Since the introduction of ART multiple case reports and case series  
137 describe new presentations of symmetrical polyarthritis clinically suggestive of  
138 Rheumatoid Arthritis. This may affect between 0.1% and 5% of HIV-infected  
139 populations, vary geographically, and presentation usually occurs after HIV  
140 suppression (9). Reveille *et al* have proposed that HIV arthritis represents a  
141 distinct self-limiting acute arthropathy affecting principally large joints (17).  
142 Ankylosing spondylitis, psoriatic arthritis and reactive arthritis occur in HIV  
143 infected populations although accurate prevalence and natural history studies  
144 are not available, with undifferentiated spondyloarthropathy commonly used as  
145 a unifying term (9).

146 HIV-associated psoriasis most commonly appears as abrupt widespread skin  
147 disease or as a severe exacerbation in patients with known psoriasis (18).  
148 Paradoxically, for pathology caused by T cell activation, psoriasis presentation is  
149 associated with increasing immunodeficiency (18). These mechanisms are  
150 poorly understood but may relate to the proportional increase in CD8+ T cells  
151 late in HIV infection that are thought to mediate skin disease (19). In advanced  
152 HIV infection, generalised skin failure is relatively more common as are co-  
153 existence of several psoriasis phenotypes (20). Unlike other inflammatory  
154 conditions in the setting of HIV infection, ART is included in formal guidance for  
155 treatment of HIV-associated psoriasis (21).

156 Of the inflammatory conditions considered in this review, there is least known  
157 about the relationship between HIV infection and inflammatory bowel disease. A  
158 recent review of the subject identified only 47 eligible patients for study across  
159 all relevant literature (22). A small retrospective case-control study suggested  
160 that HIV infection predicted lower relapse rates of all causes of inflammatory  
161 bowel disease over 18 years follow up (23). The authors speculated that  
162 impaired cell-mediated immunity may be responsible.

163 Non-biologic treatment of inflammatory conditions in HIV-infected individuals

164 We identified no randomised placebo-controlled trials evaluating safety and  
165 efficacy of any treatments for inflammatory conditions in HIV-infected  
166 individuals. The small randomized controlled studies of disease-modifying anti-  
167 rheumatic drug use in HIV-infected patients were conducted to evaluate their  
168 role as HIV therapies, they did not include patients with autoimmune diseases  
169 and the study durations were short (24–26). However, in patients with well-  
170 controlled HIV infection use of standard immunosuppression, including  
171 methotrexate for treatment of inflammatory disease, is supported with caution  
172 (9,21,27). Corticosteroids are widely used in HIV-infected individuals to treat  
173 inflammatory conditions. The metabolic and endocrine toxicity of these drugs  
174 should be monitored closely in all patients with HIV infection (28), in particular  
175 those patients receiving ritonavir-containing ART regimens, which may potently  
176 increase the action and duration of corticosteroids. Cushing’s syndrome has been  
177 reported following single injections of triamcinolone and methylprednisolone  
178 and these should not be co-administered (29).

179 **Systematic review of biologic therapies for inflammatory conditions in HIV-**  
180 **infected individuals**

181 Overview

182

183 The literature search identified two case series and 15 case reports of HIV-  
184 infected individuals receiving biologic therapy for inflammatory conditions. One  
185 further case report published after our original literature search was executed  
186 was also included (30). This represents 37 treatment episodes with 6 different  
187 biologic agents encompassing 10 inflammatory conditions (see Table 2). Two  
188 case reports describe the same individual patient over 12 years of follow up  
189 (31,32). Five treatment episodes were identified in a report of Spanish biologic  
190 registry data but no individual clinical details were available for detailed  
191 outcomes analysis (6). Only for individual patients with diagnoses of psoriasis,  
192 psoriatic arthritis and rheumatoid arthritis were more than two cases returned.  
193 Of 37 treatment episodes 33 (89%) entailed use of anti-TNF- $\alpha$  agents.

194

195 HIV diagnosis and control

196

197 For 25 individual patients with adequate clinical details, HIV acquisition  
198 preceded onset of inflammatory symptoms in seven, post-dated inflammatory  
199 symptoms in nine and in nine other patients the relative timing is unknown. Two  
200 individuals started and failed biologic therapy before HIV testing was performed  
201 (33,34). The psoriatic symptoms of both of these patients responded  
202 dramatically to ART. Besides different systemic diagnoses, the small group of  
203 patients described in the literature may also represent disparate inflammatory  
204 syndromes: individuals with recognised pre-existing inflammatory disease  
205 (35,36), occult inflammatory conditions unmasked by both HIV-mediated  
206 immunosuppression (33,37) and ART (31,32,38), and inflammatory symptoms  
207 intrinsically related to HIV infection (33,34,39). It is unknown whether these  
208 represent clinical entities that can be directly compared in a study of therapeutic  
209 efficacy.

210

211 Baseline CD4 lymphocyte count and HIV viral load values were available in all  
212 but two patients receiving biologic therapy for inflammatory conditions (Table  
213 2). The median CD4 count prior to initiation of biologic therapy was 446 cells/ $\mu$ L.  
214 Two patients developed inflammatory symptoms with advanced HIV infection  
215 and CD4 counts of 50 cells/ $\mu$ L or less. Both received only two doses of biologic  
216 therapy (33,37). Twenty patients (20/25, 80%) were established on ART at the  
217 time of commencing biologic therapy and 15 of these individuals had an  
218 undetectable HIV viral load. Two individuals commenced ART during their  
219 treatment with biologic agents. Of those established on ART before or during  
220 biologic therapy, the precise regimen was only described in 13 individuals  
221 (13/22, 59%). Two ART regimen changes were reported during biologic therapy  
222 however these were not attributed to any interaction with the biologic agent. No  
223 negative immunological or virological outcomes were described across the  
224 available literature. However CD4 count and viral load monitoring was  
225 inconsistent and often infrequent across the literature.

226

227 In a case control study of HIV-tuberculosis co-infected individuals not yet started  
228 on ART, 16 study patients received 8 doses of etanercept over 4 weeks in  
229 conjunction with routine quadruple anti-tuberculosis therapy (40). The 42 CD4  
230 count matched control patients were already receiving oral prednisolone as part  
231 of a separate trial. Even in the absence of ART only a single patient experienced a  
232 significant rise in their viral load, leading to cessation of etanercept at 2 weeks.

233

234 Efficacy

235

236 Treatment duration ranged from induction therapy of three doses to years of  
237 maintenance therapy with a median follow up of 13 months after initiation of  
238 biologic therapy. The methods of reporting treatment efficacy were variable. The  
239 largest case series of eight patients was designed as a “study of safety” and thus  
240 does not include any disease activity scores at baseline or after biologic therapy  
241 (38). In the remaining cases, specific disease activity scores were recorded at  
242 baseline and at least once after initiation of biologic therapy in only five out of 37  
243 treatment episodes (13.5%). Remission was achieved in all five cases. Where  
244 specific disease activity scores were unavailable a range of informal descriptions  
245 were used. Table 3 summarises the response of inflammatory conditions to  
246 biologic therapy: ‘unresponsive’ implies failure to respond to therapy from  
247 induction, ‘partial’ implies therapy did not reach unspecified therapeutic targets,  
248 ‘transient’ implies therapy did reach therapeutic targets but failed to sustain  
249 response, and ‘good’ implies therapy reached and sustained therapeutic targets  
250 which might include remission (Table 3). Of all treatment episodes 20/37 (54%)  
251 demonstrated a ‘good’ primary response to treatment and only 4/37 (11%) were  
252 ‘unresponsive’. Biologic therapy was stopped or switched in 14/37 (38%)  
253 treatment episodes. This rate is comparable with non HIV-infected populations  
254 (41). In these 14 instances, three were prompted by adverse events and 11 by  
255 efficacy. Etanercept accounted for 50% (7/14) of the biologic agents stopped.  
256 However Etanercept was also the most common biologic agent used across all  
257 conditions (43%, 16/37). Dosing information was available for 11 out of 37  
258 treatment episodes (30%) and largely conformed to international guidelines.

259



260 Concurrent with biologic agents 18 patients (18/25, 72%) received other  
261 synthetic disease-modifying anti-rheumatic drugs (DMARDs), including steroid  
262 therapy (14 patients) and methotrexate (eight patients). Dosing and duration of  
263 these agents was very poorly reported.

264

265

## 266 **Adverse events**

267 Analysis of adverse events described in the literature search encompassed those  
268 42 treatment episodes involving treatment of inflammatory conditions  
269 (including five patients from the Spanish biologic registry data and a total of 37  
270 treatment episodes described in other papers) and 33 treatment episodes  
271 involving treatment of HIV-infected individuals with biologic agents as trial  
272 therapy for HIV infection or tuberculosis. For those individuals where the  
273 identity of the biologic agent was known, 94% were anti-TNF- $\alpha$  agents (66/70  
274 treatment episodes).

### 275 Infectious complications

276 We identified three infection episodes requiring hospital admission that were  
277 attributed to biologic therapy: facial abscess, listeriosis, and “frequent  
278 polymicrobial infections” (37,38,42). This equates to three infectious episodes in  
279 the cumulative 50 patient-years of all biologic therapies reported in our review.  
280 This is similar to HIV-uninfected populations where relative risk of infection is  
281 reported for individual biologic agents. In the German Biologics Register RABBIT  
282 (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie) study the  
283 reported relative risk of serious infection is 2.70 for all infliximab treatment  
284 (20.59 episodes per 100 patient-years) (43). By comparison, for synthetic  
285 DMARDs in HIV-uninfected patients registry data suggests that the incidence of  
286 serious infection is 5.08 per 100 patient-years (4).

287 Given the very small case numbers, our review cannot categorically report any  
288 clear association between CD4 count at time of initiation of biologic therapy and  
289 increased incidence of infectious complications. The patient with “polymicrobial  
290 infections” had a baseline CD4 count of 50 cells/ $\mu$ L. No clinical detail is provided

291 on the nature of these infections. However, the only other patient with a CD4 cell  
292 count less than 200 cells/ $\mu$ L among patients treated for inflammatory conditions,  
293 with 29 cells/ $\mu$ L, did not develop any infectious sequelae.

294 Combined corticosteroid and DMARD use with anti-TNF therapy is associated  
295 with increased risk of infectious complications in HIV-uninfected cohorts: an  
296 odds ratio (OR) of 14.5 for combined therapy compared with 2.9 for anti-TNF  
297 monotherapy in HIV negative patients (44). All four patients identified in our  
298 review with any infectious complications attributed to biologic therapy received  
299 concomitant corticosteroid therapy. However seven other patients in our review  
300 who also received concurrent corticosteroid therapy developed no infectious  
301 complications. Corticosteroid dosing was not consistently reported.

302 Age greater than 50 years is associated with a threefold increased risk for  
303 serious infections in patients receiving anti-TNF therapies (44). Advancing age is  
304 an independent risk factor for *Listeria monocytogenes* infection in any setting  
305 (45). The case of neuroinvasive listeriosis occurred in a patient aged 69 years  
306 (42).

307 In HIV-uninfected patients, the highest incidence of infectious complications  
308 occurs within six months of starting biologic therapy (46). All infectious  
309 complications occurred within six months of initiating biologic therapy in our  
310 review. There is little discussion of antibiotic prophylaxis in the cases returned.  
311 However one individual received dapsone prophylaxis following pneumocystis  
312 pneumonia, despite a well-preserved CD4 cell count at time of biologic therapy  
313 initiation (38). In the trial of etanercept as adjuvant therapy for tuberculosis as  
314 described above, two patients, with a mean CD4 count of 394 cells/ $\mu$ L, were  
315 withdrawn after four doses of etanercept owing to increasing burden of acid fast  
316 bacilli in sputum samples (40). We did not consider this evidence of a serious  
317 adverse event nor clearly attributable to the biologic therapy. In this study there  
318 were no increased infectious complications in those 16 HIV-infected individuals  
319 receiving etanercept compared with the 42 HIV-infected control patients.

320 Non-infectious complications

321 Allergic reactions, all within the first four doses of therapy, were experienced by  
322 three HIV-infected individuals (35,38,47). Anaemia and acute anterior uveitis  
323 have been described as adverse events but no clinical detail was provided  
324 (36,38). In a recent meta-analysis of HIV-uninfected patients, biologic therapy  
325 was associated with a small increased risk of melanoma but not other  
326 malignancy. No malignant complications were identified in our systematic  
327 review. Two HIV-infected patients died during the course of biologic therapy for  
328 non-haematological indications. Both deaths occurred in patients receiving  
329 etanercept as trial therapy for non-inflammatory conditions (HIV and  
330 tuberculosis, respectively) and the cause of death, mesenteric atherosclerosis  
331 and pulmonary embolism, were not deemed to be related directly to anti-TNF- $\alpha$   
332 therapy (40,48).

### 333 **Discussion**

334 Across all organ systems autoimmune inflammatory pathology is thought to be  
335 common in HIV-infected individuals. However the understanding of the natural  
336 history of these diverse conditions in the setting of HIV infection, as well as long-  
337 term follow-up of their clinical manifestations is limited. Even for non-biologic  
338 treatment of HIV-infected patients living with inflammatory conditions there are  
339 only limited efficacy and safety data. Biologic therapies have already  
340 transformed the lives of HIV-uninfected patients with severe autoimmune  
341 conditions. For HIV-uninfected patients these agents are increasingly used by  
342 clinicians and may in the future be “gold standard” for first-line therapy,  
343 irrespective of disease severity. Therefore both current and future clinical parity  
344 for HIV-infected individuals diagnosed with inflammatory diseases warrants  
345 closer and more rigorous consideration of biologic therapy use.

346

347 Unfortunately, the available literature that specifically addresses the use of  
348 biologic agents in the treatment of HIV-infected individuals with inflammatory  
349 conditions is of poor quality. For some specific inflammatory diagnoses, such as  
350 ulcerative colitis, some available data are limited to single patient case reports.  
351 Psoriasis represents the most studied condition but only eight treatment  
352 episodes were identified in the literature. Although detailed disease scoring

353 systems were often absent, our review suggests that treatment responses were  
354 comparable to HIV-uninfected patients receiving biologic therapy. Publication  
355 bias towards positive outcomes is a legitimate concern given the small sample.  
356 Unsurprisingly there are no “control” data for inflammatory outcomes in HIV-  
357 infected individuals. Uncertainty also remains in terms of HIV control during  
358 biologic therapy. A single case-control study examining the use of biologic agents  
359 for treatment of HIV-tuberculosis co-infection in patients not receiving ART  
360 suggested that etanercept did not adversely affect HIV control. As there are no  
361 equivalent studies for individuals established on ART, suggesting biologic  
362 therapies do not adversely interact with ART currently lacks an evidence-base.  
363 However, no negative effects on ART therapy were identified in our review.

364

365 The higher quality literature pertaining to the use of biologics for haematological  
366 indications is limited, almost exclusively to rituximab, whereas guidelines for  
367 treatment of severe inflammatory conditions in HIV-uninfected groups is  
368 predicated largely on use of anti-TNF- $\alpha$  agents. Patients with haematological  
369 malignancy and lymphoproliferative disorders may also represent a relatively  
370 more immunocompromised cohort of patients and who receive concurrent  
371 chemotherapy, confounding direct comparison with patients receiving the same  
372 agents for inflammatory indications.

373

374 In summary, our systematic review highlights a paucity of good quality data on  
375 use of biologic therapies to treat inflammatory conditions in HIV-infected  
376 individuals. All evidence reviewed that addressed this clinical area directly rated  
377 very low quality according to the GRADE system (49). Due to this major  
378 limitation, the review of a cross-section of common inflammatory conditions and  
379 agents, we cannot conclude or exclude comparable efficacy and safety of biologic  
380 therapies between HIV-infected and -uninfected populations. However we feel  
381 that available data supports inclusion of HIV-infected individuals with well-  
382 controlled HIV infection in future studies of biologic therapy. There remains a  
383 broader need to study the diagnosis, natural history, and management of  
384 inflammatory conditions in HIV-infected populations. Rigorous and formal  
385 prospective data collection of this burgeoning group of patients would represent

386 a key first step to this better understanding (Table 4). [This may lead to care](#)  
387 [equality](#) for HIV-infected patients suffering from inflammatory conditions [who](#)  
388 [might benefit from biologic therapies that continue to transform](#) the [lives](#) of HIV-  
389 [uninfected individuals](#).

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