



Review

HIV/AIDS and rheumatoid arthritis

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ABSTRACT

The acquired immunodeficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV). It was first recognized in the United States in 1981, and the HIV/AIDS epidemic has since spread to affect all countries. The interface of HIV/AIDS with opportunistic infectious diseases is well characterized, but further research is required into the concurrence of other chronic diseases. The objective of this review was to identify possible interferences of HIV infection in the diagnosis and management of rheumatoid arthritis (RA). A review of the available evidence was conducted using the GRADE approach. Overall, the quality of evidence was low. Our main conclusions were: (1) the occurrence of rheumatoid-like arthritis in patients with HIV/AIDS is quite rare; therefore, it is not recommended that HIV infection be considered routinely as a differential diagnosis in this condition (C2); (2) HIV infection may lead to rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, but usually at low titers (C1); (3) RA might cause false-positive HIV serology and ELISA seems to be a more specific test for HIV in patients with RA (C2); (4) RA and AIDS may coexist, even in cases of severe immunosuppression (C1); (5) RA emergence may seldom occur during or after immune reconstitution (C1); and (6) there is insufficient safety data to recommend use of specific disease-modifying antirheumatic drugs (DMARDs) in RA patients with HIV/AIDS. Therefore, these drugs should be used cautiously (C1).

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1. Introduction

The acquired immunodeficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV). It was recognized in the United States in 1981, and, since then, the HIV/AIDS epidemic has spread to affect all countries over the past three decades [1]. By December 2011, 34 million people worldwide were living with HIV/AIDS, with more than 35 million having died of the disease [2]. HIV/AIDS has impacted global public health, with demographic, economic, cultural and political influences, especially in sub-Saharan Africa, where one-third of infected persons live [2]. Every day, 7000 new people are infected with HIV worldwide, including adults and children [2]. Since 1996, highly active antiretroviral therapy (HAART) has dramatically changed the natural history and transmission of the disease, leading to a sharp decline in global incidence. However, the high effectiveness of HIV treatment has led to a false sense of security and a consequent gradual reduction of preventive measures such as condom use [1]. Worldwide, people living with HIV/AIDS are aging, and more chronic diseases are being diagnosed in this population.

Rheumatoid arthritis (RA) is a highly prevalent autoimmune disease, affecting 0.8% of the Brazilian population [3]. This high prevalence means that RA and HIV may co-occur in some individuals. The concurrent treatment of these two diseases is a challenge, as management of RA involves immunomodulatory drugs that could potentially interfere with HIV treatment. On the other hand, the immune dysregulation inherent to HIV infection may interfere with the diagnosis of RA or mimic its clinical presentation.

The objective of this review was to identify possible interferences of HIV infection with the diagnosis and management of patients with RA.

2. Methods

A review of the literature was conducted by searching the MEDLINE, SciELO, PubMed, EMBASE, and LILACS electronic databases for articles published from January 1965 to October 2014. Findings were rated according to the level of evidence and grade of recommendation using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [4]. The level of evidence was rated as high (A), moderate (B), or low (C), and the grade of recommendation was rated as strong [1] or weak [2].

3. Results and discussion

A summary of findings is described in the Table 1.

3.1. Interference with diagnosis

3.1.1. Rheumatoid-like arthritis in patients with HIV

Rowe et al. identified rheumatoid-like arthritis in 1 out of 101 patients with HIV [5]. Hacbarth et al. did not observe rheumatoid-like arthritis in any of the 120 patients studied in the context of an outpatient infectious diseases clinic in São Paulo, Brazil [7].

In 1989, Rosenberg et al. published a radiology study of HIV patients with various forms of arthritis. Four patients were found to have radiological alterations very similar to those described in RA, such as juxta-articular osteopenia, erosions, space narrowing, and even joint deformities, but with a prominent periosteal reaction. According to the authors, these characteristics would distinguish a form of HIV-associated “pseudorheumatoid” arthritis [6]. However, these findings were not confirmed in other studies, and may have represented cases of psoriatic arthritis. In 1996, Stein et al. described the clinical characteristics of 58 patients with HIV and arthritis and identified a rheumatoid-like pattern in eight patients, but only one developed erosive arthritis, and it is unclear whether HIV infection preceded the

Table 1
Summary of Findings.

Research question	Studies	Summary of findings
Rheumatoid-like arthritis in patients with HIV/AIDS	Rowe [5]; Rosenberg [6]; Hacbarth [7]; Stein [8]; Bileckot [9]; Siqueira-Batista [10]; Varache [11]	Rheumatoid-like arthritis was rare in HIV cohorts; HIV positivity was found in one of 813 patients with undifferentiated arthritis. Nine of 198 HIV patients with arthritis presented with a rheumatoid pattern.
RF and anti-CCP positivity in patients with HIV/AIDS	Jackson [12]; Rowe [5]; Procaccia [13]; Hacbarth [7]; Silva [14]; Romic [15]; Du Toit [16]	RF, 0–55%; anti-CCP, 8–15%; both usually in low titers. IgA RF was found more often than other isotypes.
False-positive HIV serology in patients with RA	Gevorkian [17]; Li [18]	False-positive HIV serology occurred in 3.2–16% of patients with RA. ELISA showed less false-positive results than ECLIA.
Remission of RA during development of AIDS	Kerr [19]; Ornstein [20]; Ornstein [21]; Lapadula [22]; Azeroual [23]	Remains unclear, since the few reported patients with RA attained remission after AIDS while on DMARD therapy.
Development of RA during or after immune reconstitution	Calabrese [24]; Yang [25]	In prospective studies, RA emergence after HAART was found in six of 4018 patients, in an average of 67 months after HAART initiation.
Safety of DMARD use in patients with HIV/AIDS	Ornstein [21]; Aboulafia [26]; Gaylis [27]; Calabrese [28]; Bartke [29]; Calabrese [24]; Ting [30]; Sellam [31]; Kaur [32]; Linardaki [33]; Azeroual [23]; Riva [34]; Cepeda [35]; Reed [36]; Gaylis [37]; Almoallim [38]	Scarce safety data about MTX, SSZ, HCQ and anti-TNF agents; their use seems safe if HIV is controlled. No data on other DMARDs.
HIV testing before starting RA treatment	Varache [11]	No cost-effectiveness studies; As HIV is rare in patients with undifferentiated arthritis, it seems not to be cost-effective.
Interactions between antiretrovirals and DMARD	None	No known interactions between DMARDs and antiretrovirals, but data are scarce.

Anti-CCP, anti-cyclic citrullinated peptide; DMARD, disease-modifying antirheumatic drug; HAART, highly active antiretroviral therapy; HCQ, hydroxychloroquine; HIV, human immunodeficiency virus; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulfasalazine; TNF, tumor necrosis factor.

emergence of the joint symptoms [8]. In contrast, Bileckot et al. did not identify a rheumatoid-like pattern in any of a sample of 39 patients with HIV and arthritis [9]. Arthritis secondary to HIV/AIDS manifests itself more often in the form of asymmetric oligoarthritis of the lower limbs, mostly as reactive or psoriatic arthritis [10].

Varache et al. assessed patients with undifferentiated polyarthritis over a 6-week period and identified HIV positivity in only 1 of 813 patients [11].

These data suggest that the occurrence of rheumatoid-like arthritis in patients with HIV/AIDS is quite rare. On the other hand, a similar study on various lymphoproliferative malignancies showed a positive association between autoimmune and chronic inflammatory disorders, suggesting either a shared etiology/pathogenesis or a direct causal relation [39].

Several antiretroviral drugs were associated with occurrence of arthralgia in clinical studies, including lamivudine, didanosine, nevirapine, tenofovir, indinavir, saquinavir, lopinavir/ritonavir, and maraviroc. However, none was associated with arthritis [40]; therefore, this adverse effect is easily distinguishable from RA manifestations.

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