Review

HIV/AIDS and rheumatoid arthritis

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A B S T R A C T

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 (C1); (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 emergence may seldom occur during or after immune reconstitution (C1); (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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Contents

1. Introduction ............................................................... 0
2. Methods ................................................................. 0
3. Results and discussion .............................................. 0
3.1. Interference with diagnosis ...................................... 0
3.1.1. Rheumatoid-like arthritis in patients with HIV ........ 0
3.1.2. Positivity of RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies in patients with HIV/AIDS .................. 0
3.1.3. False-positive HIV serology in patients with RA ....... 0
3.2. Interference with treatment ....................................... 0
3.2.1. Remission of RA during development of AIDS .......... 0
3.2.2. Development of RA during or after immune reconstitution ................................................................. 0
3.2.3. Safety of DMARD use in patients with HIV/AIDS ..... 0
3.2.4. HIV testing before starting RA treatment .............. 0
3.2.5. Interactions between antiretrovirals and DMARDs ... 0
4. Conclusions ............................................................. 0
5. Financial disclosure .................................................... 0
6. Conflict of interest ...................................................... 0
7. Take-home messages ................................................... 0
8. Acknowledgments ...................................................... 0
9. References ............................................................... 0

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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]. Hachbarch et al. did not observe rheumatoid-like arthritis in any of the 120 patients studied in the context of an outpatient infectious disease 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 periostal 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 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 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 [36].

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Table 1

| Summary of Findings. | |
|---------------------|------------------|------------------|
| Research question   | Studies           | Summary of findings |
| Rheumatoid-like arthritis in patients with HIV/AIDS | Rowe [5]; Rosenberg [6]; Hachbarch [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. |
| RF and anti-CCP positivity in patients with HIV/AIDS | Jackson [12]; Rowe [5]; Procacci [13]; Hachbarch [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 | Gegovkian [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]; Ornest [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 | Ornest [21]; Aboulaifa [26]; Gaylis [27]; Calabrese [28]; Bartke [29]; Calabrese [24]; Ting [30]; Sellam [31]; Kaur [32]; Lardardaki [33]; Azeroual [23]; Riva [34]; Cepeda [35]; Reed [36]; Gaylis [37]; Almosallim [38] | Scarce safety data about MTX, SSZ, HCl and anti-TNF agents; their use seems safe if HIV is controlled. |
| 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; HCl, hydroxychloroquine; HIV, human immunodeficiency virus; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulfasalazine; TNF, tumor necrosis factor.

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3.1.2. Positivity of RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies in patients with HIV/AIDS

In 1980, Jackson et al. identified elevated IgA rheumatoid factor (RF) in 26% of male homosexual patients with AIDS, and their antibody levels were higher than those of controls, although in low titers. All groups showed similar IgM positivity [12]. Procaccia et al. reported IgA positivity in up to 55% of male homosexual AIDS patients, a rate higher than that observed in asymptomatic carriers of HIV, but IgG and IgM titers were similar between groups [13]. In 2006, Silva et al. identified RF positivity in three patients and anti-CCP antibodies in one of 12 Brazilian patients with HIV/AIDS [14], but, in both cases, with much lower titers than controls with RA. These data were confirmed by a study conducted in Croatia [15]. Recently, du Toit et al. found positive IgG RF and anti-CCP antibodies in 47% and 15% of patients with HIV/AIDS respectively, although most patients had low titers [16]. In the same study, a lower percentage of positive tests and antibody titers after 6 months was found among patients who initiated HAART, proportional to the increase of CD4+ lymphocytes. No patients developed RA within 1-year follow-up [16]. Telles et al. found RF positivity in 10% of 69 Brazilian patients with AIDS in a 2012 study, but there is no description of the titers. This prevalence was lower than that reported in older studies [41]. Two other studies did not observe higher antibody positivity in patients with HIV/AIDS [5,7]. Differences between studies may be explained by differences in populations and methods of antibody detection (in the case of RF) and by the fact that the studies were performed in very distinct eras — some were conducted in the pre-HAART era, while others are more recent.

3.1.3. False-positive HIV serology in patients with RA

Geworkian et al. identified false-positive antibodies against the p41 antigen of HIV in 1 of 31 Mexican patients with RA, using ELISA, a rate considered similar to that of the general population [17]. In contrast, Li et al. found false p24 antigen, anti-HIV-1, or anti-HIV-2 positivity by electrochemiluminescence immunoassay (ECLIA) in 16% of Chinese RA patients, while no patients had false-positive results with ELISA [18].

3.2. Interference with treatment

3.2.1. Remission of RA during development of AIDS

It is unclear whether the development of AIDS might lead to remission of RA. In some cases, remission occurred after the development of AIDS, while in others the two conditions coexisted, even under severe immunosuppression [19–22]. A review published in 1995 reported that all patients with HIV/AIDS and RA in which remission occurred only after progression to AIDS had been treated with DMARDs [23].

3.2.2. Development of RA during or after immune reconstitution

A cohort of patients with HIV/AIDS has been monitored for over 20 years by Calabrese et al. in an attempt to detect the onset of rheumatologic manifestations. Among the 395 patients who were assessed in pre-HAART era, no patient developed RA [24]. However, a systematic review conducted by the same authors identified two cases of RA in patients with AIDS, whose initial presentation occurred shortly after initiation of HAART, during the immune reconstitution phase [24].

In 2013, a review of medical records of 3623 patients with HIV/AIDS at a university hospital in Taiwan identified concomitant diagnosis of RA in six (0.16%) cases. Among these, five patients developed arthritis after the initiation of HAART, with an average time to onset of arthritis of 67 months [25].

Jordache et al. reviewed 52 patients with HIV and autoimmune diseases in 14 medical departments in Île-de-France and found 5 cases of RA, 3 of which had their initial presentation after HIV diagnosis [42].

The mean duration of follow-up of these patients and which treatments they received are unclear.

Siva and Brasington described the case of a patient with HIV polyarthralgia which progressed to full-blown RA after initiation of HAART [43].

3.2.3. Safety of DMARD use in patients with HIV/AIDS

Most available data regarding the safety of the use of DMARD in HIV/AIDS patients comes from case series.

3.2.3.1. Methotrexate. Early in the AIDS epidemic, there were reports of rapid progression to AIDS after treatment with methotrexate (MTX), with development of opportunistic infections, as well as other reports in which no such adverse effect occurred [24]. However, these articles did not clearly describe the progression of CD4+ lymphocyte counts and viral load after initiation of MTX treatment. Furthermore, the life expectancy of patients with AIDS was 40 months at the time of these reports [24], as highly active antiretroviral regimens were not available. Therefore, these patients might have had unfavorable outcomes even if they had not been on MTX.

3.2.3.2. Hydroxychloroquine. In three cases, hydroxychloroquine was used in patients with AIDS associated with spondyloarthritis or RA. There were no opportunistic infections [21,23] and in one case there was a 1-log reduction in viral load [21], although there was a decline in CD4+ lymphocyte count in both cases. One patient achieved remission after starting treatment [21]. Hydroxychloroquine might be an option for the treatment of RA in patients with HIV.

3.2.3.3. Sulphasalazine. In 1991, Disla et al. described three patients with HIV and reactive arthritis who received sulphasalazine (SSZ) therapy without concomitant antiretroviral drugs. All patients had significant improvement of CD4+ lymphocyte counts after several months [44]. SSZ has immunomodulatory effects that may be favorable in the context of HIV infection, such as inhibition of NF-κB migration to the nucleus of T lymphocytes [34]. Furthermore, it induced significant reduction of viral infectivity in vitro when added to indinavir in comparison with the protease inhibitor alone [45]. Therefore, SSZ may also be an option for the treatment of RA in patients with HIV.

Aromatic sulfonamides with amine functional groups (sulfamethoxazole, sulfadiazine) are often involved in allergic reactions in patients with HIV/AIDS, with an incidence rate of up to 60%. However, the incidence of cross-reactivity between sulfonamides and non-aromatic amines (such as SSZ) is low [45].

3.2.3.4. Leflunomide. A double-blind randomized trial conducted by Read et al. evaluated leflunomide (LFN) treatment in asymptomatic individuals with HIV [36]. After 28 days, the viral loads and CD4+ lymphocyte counts of patients on the drug remained stable compared to those of placebo recipients, although serum levels of LFN were low compared to those of patients on RA therapy [35]. There are no reports on treatment with LFN in RA patients with HIV.

3.2.3.5. Tumor necrosis factor antagonists. Since the comorbidity occurrence of HIV/AIDS and RA appears to be rare [28], most reports of tumor necrosis factor antagonist (anti-TNF) therapy involve patients with psoriasis or psoriatic arthritis. Cepeda et al. described the outcome of two patients with RA who were treated with etanercept (ETN) for 12 to 50 months, alongside six other patients with spondyloarthritis [35]. ETN had been used in all patients, infliximab in four, and adalimumab (ADA) in three. All, except one, were already on other DMARDs previously. Five patients were on HAART, and no change of HIV treatment was necessary in any case. In all cases, viral load and CD4+ lymphocyte remained stable. None of the patients had serious infections during the follow-up period [32].

Abulafia et al. described a patient with HIV and RA, on HAART, who was treated with ETN to good effect, with good virological and immunological parameters [26,32].

In other reports of HIV patients on anti-TNF therapy for spondyloarthritis, only Abulafia et al. described the occurrence of multiple polymicrobial infections during ETN therapy [26]. However, the patient in question was diagnosed with advanced AIDS and was severely immunosuppressed at the time of treatment. Furthermore,
HIV infection may lead to RF and anti-CCP positivity, but usually at low titers (C2). The occurrence of rheumatoid-like arthritis in patients with HIV/AIDS is quite rare. Therefore, it is not recommended that HIV infection be considered as a routine differential diagnosis in patients with this condition (C2).

RA may cause false-positive HIV serologies. ELISA might be a more specific test than ECLIA for HIV in patients with RA (C2).

RA and AIDS may coexist, even in cases of severe immunosuppression (C1). RA may seldom emerge during or after immune reconstitution (C1). There is insufficient safety data to recommend any specific DMARD in RA patients with HIV/AIDS; therefore, these drugs should be used cautiously (C1). With the recent recommendation of universal HAART therapy in HIV-positive patients in some countries, more patients will be exposed to antiretroviral drugs worldwide regardless of immunological and virological parameters. Interactions between HIV/AIDS and comorbid chronic diseases will have to be considered within this approach.

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