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# Challenges of Rheumatoid Arthritis Management in Sub-Saharan Africa in the 21st Century

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## Abstract

In recent decades, several advances have been made in the management of rheumatoid arthritis (RA) both in the diagnostic field and in the therapeutic field. Unfortunately, RA remains poorly studied in black Africa. Epidemiological data are rare and controversial. The estimated prevalence of RA in Africa is about 0% - 2.54%. Risk factors associated with RA must be studied by taking into account special features of black Africa such as the low tobacco consumption in certain regions, the tropical climate and the high frequency of endemic parasitic and viral infections. The initially supposed mildness of RA in black Africa is increasingly challenged. The diagnosis is often made too late because of the scarcity of rheumatologists and ignorance. Diagnostic tools are limited to the clinical data, the erythrocyte sedimentation rate and radiographs as the other tools are poorly available. In addition, there are misconceptions in African communities, responsible for loss of sight during follow-up and treatment discontinuations. This is exacerbated by the shortage of disease-modifying anti-rheumatic drugs (DMARDs) and the inability to afford them. Furthermore, biological agents are very difficult to access. Further studies are essential to better understand the characteristics of RA in black Africa. Thus, collaborations between African and Western research teams seem very important. In order to make available the DMARDs especially biological agents, pharmaceutical companies can contribute through research partnerships. Moreover, governments should provide a better place for chronic inflammatory diseases in the programs against non-communicable diseases. Finally, training must also be promoted to increase the number of specialists and the level of knowledge of other health workers.

## Keywords

Rheumatoid Arthritis, Black Africa, Rheumatoid Factor, Anti-Cyclic

Citrullinated Peptide Antibodies

## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease characterized by joint swelling, joint tenderness and destruction of synovial joints, leading to severe disability and premature mortality [1]. Few data are available on RA in black Africa. It was suggested that in black population, inflammatory polyarthritis was much less common and much milder in its manifestations than in European and American peoples [2]. However, new publications indicate an increase in the prevalence and severity of RA in black Africa. Moreover, the reported epidemiological data are highly variable. Now, chronic inflammatory diseases such as RA are not part of the priority issues in sub-Saharan Africa. So, RA is diagnosed too late and inadequately treated [3]. This review aims to describe the status of the management of RA in black Africa.

## 2. Epidemiology

### 2.1. Prevalence Data

The prevalence of RA is variable worldwide from 0.3% to 1.2% according to the geographical region [3] [4]. RA is the most frequent chronic inflammatory rheumatism in western countries where its prevalence is estimated to 0.5% - 1% of adults [5] [6] [7] [8]. An annual incidence of 5 to 50 cases for 100,000 adults is reported [8] and this incidence arises with the age. Women are more affected by RA [8] [9]. In United Kingdom (UK), Symmons *et al.* reported in 2002 a prevalence of 1.16% in women against 0.44% in men [10]. The role of hormonal factors in this susceptibility of women is not proven [5].

There is lack of epidemiological data on RA in black Africa. Alamanos *et al.* noticed in 2006 that incidence studies were not available from developing countries [11]. A prevalence of 0% - 0.3% has been reported in Africa [5] [11] but the extent of the problem caused by RA in Africa is presently uncertain, as very few epidemiological studies have been conducted [12]. Some studies concerned blacks living abroad especially in western countries while other studies have been conducted in people living in Africa. The general impression is that RA has a lower prevalence and a milder course in developing countries, especially in black Africa [7] [12]-[18].

#### 2.1.1. Data from Blacks Living in Western Countries

In order to assess the impact of the race on the prevalence of RA in UK, MacGregor *et al.* had compared Black-Caribbeans to Whites living in Manchester, a same urban area. They have clearly shown that RA was less common in Blacks (0.29%) than in Whites (0.8%), emphasizing the important role played by genetic factors in the onset of the disease [19]. In Colombia, Anaya *et al.* had estimated that the hospital incidence of RA for 1995 was 0.65 cases per 1000 persons

and the period prevalence in the general population was 0.01% in African Colombians [13].

#### 2.1.2. Data from Studies Conducted in People Living in Africa

The literature would suggest that the first reported case in Africa has only been described in 1956, since when an increasing number of cases have been identified across Africa [12]. In South Africa, Beighton *et al.* have shown through an epidemiological study of a rural African community (n = 801) that there was no case of active rheumatoid arthritis in the entire population investigated. The prevalence of "definite" rheumatoid arthritis was 0.12%, and of "definite" and "probable" rheumatoid arthritis combined, 0.87% [2]. In Togo, Houzou *et al.* found that in 16 years retrospective study 626 (4.63%) cases of both chronic inflammatory rheumatisms and connective tissue diseases. Out of these 626 cases, 399 (63.7%) were undifferentiated rheumatism whereas 62 (9.9%) were RA [20]. RA represented 0.46% of the overall rheumatic diseases in this study. Thus, the prevalence of RA would be less than 0.46% in the general population of Togo. The large number of undifferentiated rheumatism in this study reflects the difficulties in diagnosis and classification of rheumatic diseases.

Recently, two systematic reviews have been published in order to assess epidemiological data in Africa. The first, from Dowman *et al.* concerned RA especially while the second, from Usenbo *et al.* concerned six types of arthritis including RA. The prevalence of RA in Africa had been estimated by Dowman *et al.* to 0.36% in 1990 and extrapolated to 0.42% in 2010. Paradoxically, a very high prevalence of 2% has been reported in Jamaica. This review concerned 10 population-based studies and 11 hospital-based studies. Only two new population-based studies have been found by Dowman *et al.* from 1990 to 2010, so that the projected prevalence may be uncertain. The authors had underlined the fact that their review includes North Africa whose background is different from that of sub-Saharan population [12]. In their review on arthritis prevalence published in 2015, Usenbo *et al.* have identified the paucity of latest prevalence data on arthritis in Africa. Fourteen of the included studies (14/27, 52%) were published from 2001 to date, emphasizing the paucity of data on arthritis prevalence in Africa [21]. The majority of the studies were from South Africa (12/27; 44.4%). The prevalence of RA ranged from a minimum of 0.13% in Algeria, 0.6% in the Democratic Republic of Congo (DRC), to a maximum meta-analysis result of 2.54% in South Africa. The overall prevalence could not be assessed because of the wide range of prevalence found [21].

In Nigeria, Adelowo *et al.* reported retrospectively, results from the first 200 RA patients presenting to a private rheumatology clinic in Lagos. These results showed that RA is not uncommon among Nigerians, accounting for 12.3% of a total of 1623 patients presenting to the clinic [22]. Data from recent studies would suggest higher prevalence of RA. In DRC, Malemba *et al.* reported in 2008 a retrospective and hospital-based study including 2370 rheumatic patients attending the Rheumatology clinic at University Hospital of Kinshasa from 1988

to 2002. Compared to the previous studies performed in the same hospital, the results of this study disclose a threefold increase of rheumatic outpatients. RA was the most frequent autoimmune disease in this study accounting for 67.8% of all autoimmune diseases and 3.5% of all rheumatic diseases [16].

These highly variables data may relate to different times and in different conditions in which the studies had been conducted. This not allows drawing a valid conclusion about the real prevalence of RA. Thus, further large multicenter studies are needed.

### 2.2. The Scarcity of Epidemiological Data in French Speaking Countries

When analyzing epidemiological data on RA in black Africa, it appears that all the studies carried around 1970 and 1980 underline the requirement of new population-based studies. Unfortunately, these studies are decreasing in black Africa since 1990. Thus, in their review, Usenbo *et al.* noted the same problem in 2015 [21]. This could be due to funding problems. The scarce resources available are allocated to infectious diseases such as malaria, HIV and tuberculosis. Thus, a large number of data are obtained from hospital studies. Available studies are generally from a limited number of countries. Of the 10 population-based studies reviewed by Dowman *et al.* in 2013, 6 were from South Africa, 1 from Nigeria, 1 from Lesotho, 1 from Uganda and Liberia and the last one from Egypt [12]. None study was conducted in French-speaking country. The few publications available from sub-Saharan French-speaking countries are essentially from five countries: Burkina-Faso, Cameroon, DRC, Senegal and Togo. These publications rarely report prevalence or incidence data. The review of Usenbo *et al.* published in 2015 includes 5 studies (out of the 27 studies) from french-speaking countries: 3 from Cameroon, 1 from DRC and 1 from Burkina-Faso. The study from Burkina-Faso was related to infectious disease as it was carried in HIV-infected patients undergoing highly active antiretroviral therapy (HAART) [21].

## 3. Risk Factors

The cause of RA is still unknown but a large number of risk factors have been reported including genetic and environmental and patient associated factors [6] [8]. These risk factors can be categorized into patient related factors and environmental factors.

### 3.1. Patient Related Factors

#### 3.1.1. Genetic Factors

Several genetic factors are suspected of being associated with the development and the course of RA. The human leukocyte antigen (HLA) especially HLA-DRB1 Shared Epitope (SE) is the strongest of them [23]. So, the following data and comments will be focused on this SE.

**1) The Shared Epitope in Western countries**

Relying on a study of twins with RA, MacGregor *et al.* have shown that genet-

ic factors accounted for approximately 60% in the susceptibility to develop RA [24]. A nested case–control study performed in Sweden showed that the sensitivity for SE as a diagnostic indicator for RA was 60%. In the same study, the authors demonstrated that the presence of anti-cyclic citrullinated peptide antibodies (ACPA or anti-CCP Abs) together with SE gene carriage is associated with a very high relative risk for future development of RA [25].

The SE is associated not only with increased susceptibility to the occurrence of RA but also with greater severity of RA. This severity is characterized by a greater joint destruction in patients who carry the SE as reported by the study of Kazkaz *et al.* including patients from Syria and France. In addition, a dose effect was observed in the involvement of the SE in the pathogenesis of RA. The disease risk was higher in patients with two copies of SE than in those with one copy of SE in both Syrian and French patients. In the same study, the authors also showed that SE was more common in French (62.7%) than in Syrian (39.7%) patients. In Syrian patients, the different HLA-DRB1 alleles do not seem to have the same impact on the disease as that is observed in the French patients. This suggests that the same allele can have different roles depending on the ethnicity of the patient [26].

The SE is involved, at least in Western patients, in susceptibility to produce ACPA [27]. However, HLA-DRB1 alone especially with its SE does not appear to fully explain the pathogenesis of RA, it is suggested that other genetic factors may play a role in the onset and progression of RA [26]. It is known that the SE is less frequent in Blacks than in Whites. This has been shown in Americans where blacks and whites live in the same environmental conditions [28] [29]. The HLA-DRB1 * 0401 and *0404 are the most frequently encountered among European patients with RA [30]. The RA-associated HLA-DRB1 * 0404 allele was the most strongly associated with the presence of ACPA in RA sera from Marseille [31].

**2) The Shared Epitope in black Africa**

Most of the time, the HLA-DRB1 SE typing is performed in black African patients in a research context as this test is unavailable. Thus, it is performed in western countries through a partnership with western research teams. The frequency of the SE in black African RA patients range from 30% to 92% but most of the available studies provide low frequencies as shown in **Table 1**. If the correlation of the SE with increased susceptibility to develop RA remains valid within Blacks, Malemba *et al.* hypothesized that the low prevalence of this epitope suggests that there would be other genetic factors, different from the HLA-DRB1 shared epitope, which are involved in Congolese patients besides different environmental factors [32]. Otherwise, sometimes similar prevalence of ACPA in black Africans compared to Caucasians contrast paradoxically with the low percentage of SE in black patients. This suggests that other genetic parameters could be involved in susceptibility to produce ACPA in black Africans [18]. Among African Blacks, HLA-DRB1 alleles which carry the SE don't have the same distribution as in Caucasians. Indeed, unlike Caucasian patients, HLA-

**Table 1.** The prevalence of HLA Shared Epitope in different populations worldwide.

| | Area (km²)/ Population (n) | Number of participants (n) RA/HI* | HLA-SE (%) RA/HI | Reference number |
|---|---|---|---|---|
| **Africa** | | | | |
| South Africa[£] | 1,219,912/51,770,560 | 143/- | 92/- | [38] |
| DRC | 2,345,409/81,680,000 | 37/24 | 35.1/12.5 | [32] |
| Cameroon | 475,442/20,386,799 | 56/50 | 30/10 | [18] |
| **Western** | | | | |
| France | 675,000/67,107,000 | 512/471 | 62.7/38.4 | [26] |
| Sweden | 449,965/10,508,669 | 57/- | 60/- | [25] |
| UK | 246,690/67,886,004 | 404/286 | 59/44 | [29] |
| Syria | 185,180/22,339,300 | 156/120 | 39.7/23.3 | [26] |

*HI: healthy individuals; [£]86.7% of blacks were included in this study.

DRB1 * 0401 is less common among blacks. This allele has been described as the allele associated with the most severe forms of RA [33] [34]. In Congolese patients, Malemba *et al.* reported a low frequency of HLA-DRB1 * 0401. This low frequency may partially explain the mildness of the disease in Blacks [32]. In United Sates of America (USA), Hughes *et al.* showed in a multicenter cohort study among African Americans that the SE was more frequent in patients with RA than in control subjects. The finding of a higher degree of European ancestry among African Americans with SE alleles suggests that a genetic risk factor for RA was introduced into the African American population through admixture, thus making these individuals more susceptible to subsequent environmental or unknown factors that trigger the disease. They concluded that genetic admixture is responsible of increase risk to develop RA by African American [35].

The SE would be also less common among Asian patients. Chun-Lai *et al.* reported in RA patients from Malaysia an heterogeneous frequency of SE with 36.0%, 34.3% and 48.3% respectively among the Malays, Chinese and Indians. Furthermore, the HLA-DRB1 * 0405 is the most frequently encountered allele in patients from East Asia [30] [36] [37] while in Europeans, the alleles mostly encountered in RA patients are DRB1 * 0401, *0404 and *0408 [36]. Due to racial heterogeneity found in the expression of SE alleles, it seems important to undertake further studies in black Africa to better understand the role of the SE in the onset and course of RA.

### 3.1.2. Age

In a population-based study conducted in DRC in 2010, Malemba *et al.* reported a RA prevalence of 0.6% in the urban population of Kinshasa. This prevalence goes up to 0.9% if applied only to adults older than 18 years because the prevalence increases with age. The authors concluded that the prevalence of RA in

Congolese urban population is similar to that found in occidental general population [39]. Because there is more young people in sub-Saharan populations, it can be suggested that the prevalence of RA is diluted by the youth population [40].

#### 3.1.3. Sex

As known in western countries, RA is also more frequent in women in black Africa [6] [8]. **Table 2** indicates different proportions of women reported. The predominance of RA in women indicates that the female gender is a risk factor for developing this disease. There is no explanation for this predominance but hypothesis had been made including reproductive hormones.

### 3.2. Environmental Factors

#### 3.2.1. Smoking

Tobacco is the most mentioned environmental factor as doubling the risk [8] [45] [46]. In USA, Mikuls *et al.* showed that cigarette smoking is associated with both subcutaneous nodules and higher serum concentrations of IgA rheumatoid factor (RF) in African Americans with RA [47]. This has also been demonstrated in south African patients [48]. In many regions of black Africa there is few smokers and the major part of them are men. However, RA is more frequent

**Table 2.** The proportions of women in various studies on rheumatoid arthritis.

| | Area (km²)/ Population (n) | Number of participants (n) | Percentage (%) of women | Reference number |
|---|---|---|---|---|
| **Africa** | | | | |
| Cameroun | 475,442/20,386,799 | 56 | 95 | [18] |
| DRC | 2,345,409/81,680,000 | 128 | 89.1 | [32] |
| Senegal | 196,722/14,354,690 | 205 | 88.2 | [41] |
| Togo | 56,785/6,191,155 | 62 | 83.8 | [20] |
| South Africa | 1,219,912/51,770,560 | 120 | 83 | [42] |
| South Africa | 1,219,912/51,770,560 | 143 | 82.5 | [38] |
| Burkina Faso | 274,200/18,365,123 | 42 | 81 | [43] |
| Nigeria | 923,768/182,202,000 | 200 | 70.5 | [22] |
| **Western** | | | | |
| USA | 9,629,048/320,206,000 | 20,609* | 75.72 - 85.92[£] | [44] |
| Syria | 185,180/22,339,300 | 156 | 80.1 | [26] |
| France | 675,000/67,107,000 | 260 | 78 | [31] |
| France | 675,000/67,107,000 | 512 | 74.8 | [26] |

*White (n = 17,687); African American (n = 1492); Hispanic (n = 1095); [@]Asian (n = 335). [£]White (75.72%); African American (83.98%); Hispanic (80.90%); [@]Asian (85.92%).

in women like that is found in western countries. In Congolese patients with RA, Malemba *et al.* reported moderate tobacco consumption, so that only 2 male were smokers out of the 128 patients including 14 males [32]. In the study conducted in Cameroon by Singwe-Ngandeu *et al.*, only one of the 56 patients was smoker [18]. The majority of African people culturally admit that women should not smoke. Women who smoke are considered to have a bad morality. Because women are more affected by RA although they don't smoke, it seems appropriate to look for other environmental factors that might be involved in the onset of RA in black Africa [18].

#### 3.2.2. Living Environment

The prevalence of RA might be lower in rural population than in urban one [5] [7]. The low prevalence of RA in rural area suggests that urbanization and industrialization increase the disease risk. The limited data available appear to show an increasing prevalence and severity of RA in Africa, particularly for urban populations [7] [12] [40] [49]. One explanation for this is the transition to an urban lifestyle in most developing countries with its consequences such as sedentary lifestyle, cigarette smoking and high sugar and calorie diets, obesity and other cardiovascular hazards [50]. The urban–rural differences in prevalence strongly suggest a role for an environmental agent in the pathogenesis of RA, but no causes have been conclusively identified to explain this variation in prevalence.

#### 3.2.3. Infectious Diseases

The role of infectious diseases in the onset of RA in black Africans must be studied with particular attention as there are many endemic infectious diseases in Africa. Indeed, some data reported that RA might be triggered by infectious agents such as parvovirus, rubella virus, Epstein–Barr virus, *Borrelia burgdorferi*, and others [5]. Immunization has also been suspected as responsible of the onset of RA [51]. In contrast with previous hypothesis, it has been reported that infectious diseases, particularly chronic parasitic infections may protect from RA [52]-[57]. The first results in favor of parasitic protection were from Greenwood who had made several assumptions. He suggested that the infrequent occurrence of autoimmune disease in parts of tropical Africa is related to the immunological disturbance produced by multiple parasitic infections. The manner in which parasitic infections could interfere with the appearance of autoimmune disease remains a matter for speculation. Repeated parasitic infections may have some protective action against the development of autoimmune disease [52]. It has been experimentally demonstrated that ES-62, a molecule secreted by the parasitic filarial nematode *Acanthocheilonema viteae*, protects mice from developing collagen-induced arthritis [56]. Mice infested by *Plasmodium falciparum* were protected against autoimmune diseases in the experiment made by Greenwood *et al.* [58]. It has been postulated that tropical infections might confer protection against the development of RA. The improvement in health care, with loss of the

protection of such infections, has been implicated in a possible increase in the prevalence and severity of RA in urban area [15]. The protective role of infectious agents can be included in the "hygiene hypothesis" according to which the improvement of environmental hygiene prevents exposure to microorganisms when this exposure is necessary to "educate" the immune system so that it can respond appropriately. Without this exposure, the immune responses end up being so inadequate that they contribute to the development of dysimmune diseases, including hypersensitivities and autoimmune diseases including RA. It has been also suggested that RA is triggered by an interaction with an unknown infectious agent introduced in urban population, and it would explain rare occurrence in rural populations [12]. No study has defined a direct relation between one pathogen leading to one disease [59]. Thus, the real role of infectious agents in the onset of RA is unclear.

#### 3.2.4. Other Environmental Factors

Many other environmental factors have been reported including alcohol, coffee, vitamin D, meat eating, oral contraception, maternal breasting, born body weight and bad socio-economic conditions but the level of implication of these factors is low or uncertain [5] [60]. The role of tropical climate as protective factor has been also reported [14] [53].

## 4. Clinical Features

### 4.1. The Severity of RA in Black Africa

In addition to its rarity, RA was also thought to have a mild course in black Africans. This mildness of RA reported in black Africans is related to the absence or rarity of nodules and systemic manifestations [7]. In Nigerian patients, Adelowo *et al.* found that subcutaneous nodules were seen in 29.5% of the cases. This is over the 20% usually reported. No vasculitis was found. Radiographs of the hands of 106 patients showed 29.2% of erosive changes that were mostly mild [22]. In the same way in Nigeria, Greenwood *et al.* reported in 1969 that extensor nodules, found in approximately 30% of European RA patients were found in only 5.6% of Nigerians. A low incidence of vascular lesions and peripheral neuritis was also found. Radiological changes were mild, and the prognosis was good. It is suggested that the patients had a distinct form of chronic polyarthritis which has an etiology related to the tropical environment or that they had rheumatoid arthritis modified in some way by the tropical environment [14].

In Colombia, Anaya *et al.* reported lower erosion scores in African Colombian patients (n = 18) compared to Mestizos (n = 56) [13]. Through an epidemiological study of a rural African community (n = 801) of South Africa, Beighton *et al.* showed that inflammatory polyarthritis was much less common and much milder in its manifestations than in European and American peoples [2]. In DRC, Malemba *et al.* reported in RA patients that typical joint deformities were

observed in 11 patients (21.6%) and extra-articular manifestations (rheumatoid nodules, sicca syndrome, and anemia) in 8 patients (15.7%) [61]. The same authors explained the less severity of RA in their patients in another retrospective and hospital-based study by the paucity of erosive arthritis and extra-articular manifestations. In this study conducted in 2008, joint deformities were rare comparatively to the European and American figures where they are common and may require surgical reparations [16]. The low prevalence of extra-articular manifestations and erosive changes on radiographs suggest that RA runs a milder course among African populations [22] [49].

However, the mildness of RA in black Africa is increasingly challenged by new data [41]. In South Africa, Hodkinson *et al.* reported 18.3% of rheumatoid nodules in 120 blacks with early RA. The mean duration of the disease was 11.9 months. The overall group had very active disease as reflected by a mean DAS28 of 6.2. The disease was erosive in 46% of cases. The authors stated that severe disease at presentation, at least in part, is a reflection of delay in referral for tertiary care [42]. In the same way, a recent study including 128 RA patients from DRC, showed that DAS-28 at first visit was higher than 5.1 and HAQ ≥ 0.5 in all patients. X-rays showed joint erosions and/or joint space narrowing, mostly of a moderate grade in 55.8% [32]. In the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort (n = 813) from France, DAS-28 at first visit was >5.1 in 48% of patients [62]. In their study comparing rural to urban patients with RA, Lekpa *et al.* in Senegal suggested that the diagnosis of RA in rural areas may certainly be underestimated because there are few specialists, accessibility to health facilities is more difficult and the diagnosis of RA itself may be mistaken. One interesting point was the higher frequency of extra-articular manifestation in patients from rural areas which is known to be a factor of poor prognosis [63]. However, it could be hypothesized that only severe cases from rural area are referred to specialists. Thus, mild cases from rural area do not visit hospital. This could explain the high frequency of extra-articular manifestations.

New prognostic factors are currently under investigation. So, in Western populations, an important cause of the increased mortality in RA is cardiovascular complications resulting from the disease and iatrogenic factors. Through a systematic review, Meune *et al.* showed that RA is associated with a 60% increase in risk of cardiovascular death compared with general population suggesting that targeting a reduction in cardiovascular mortality should still be considered as a major issue in RA [64]. In contrast, infections are probably the most common cause of death in the developing world, although there are no published data on the causes of death in RA patients from the developing world [15]. To date, cardiovascular complications have been little studied in black Africa [65]. However, it is clear that the incidence of cardiovascular disease is constantly increasing in black Africa.

### 4.2. Constraints against RA Management in Black Africa

There are several constraints that affect RA management in Africa. Some con-

straints are delayed diagnosis, lack of resources and problems related to long-term monitoring. The first visit is often delayed due to ignorance or misconceptions and also to scarcity or inaccessibility of rheumatologists [22] [41]. Patients with RA in black Africa and Middle East are often diagnosed late, present with active disease and often do not receive disease-modifying anti-rheumatic drugs (DMARDs) early in the course of the disease [3]. In Nigerians, Adelowo *et al.* found that the mean duration of symptoms before presentation was over 5 years, exactly 63.4 months [22]. Similarly, in DRC, Malemba *et al.* reported in Congolese RA patient's delays from symptom onset till their first visit of 3.2 to 4 years [32] [61]. The delayed diagnosis is a great threat to the course of the disease. Indeed, the French cohort named ESPOIR indicates that among patients with inflammatory arthritis in daily clinical practice, early initiation of DMARD therapy reduces 12-month radiographic progression [66].

Another important problem encountered with prospective cohort studies in Africa is the large number of lost to follow-up. This situation relies on the chronicity of RA. For example, out of 98 patients under methotrexate recruited by Malemba *et al.* for a prospective study in DRC, over one third (36.7%) was lost to follow-up over a period of 20 months [61]. In Senegal, during the first 6 months of treatment with DMARDs, patients had a mean of 4 clinic visits, and 48% of the 205 patients missed at least one scheduled visit [41]. In another study from Senegal, Ka *et al.* reported results of 12 patients from Dakar followed during 6 - 7 years. The treatment was discontinued in 3 patients for non-compliance and four others were lost to follow-up [67]. As with other chronic diseases, there are many misconceptions in African communities. Any incurable disease is too often seen as linked to the action of evil spirits. This belief is maintained by quacks and traditional healers. So, it is clear that any action of evil spirits cannot be cured by modern medicine. It is therefore necessary to resort to mystical action. Malemba *et al.* suggested that in Central Africa there is a real need for a better understanding of patients' misperceptions of chronic diseases [61].

Furthermore, ignorance and lack of financial resources lead patients not to respond to the appointment of the doctor when symptoms disappear. Finally, as in developed countries, chronic diseases are responsible for a nomadism of patients who are always looking for the most competent doctor.

## 5. Biological Tests Used in the Management of RA

Some biological tests are needed for diagnosis and/or follow-up of RA. These tests include inflammatory tests such as Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP), auto-immunity tests such as RF and ACPA and genetic susceptibility tests especially the HLA-SE. Most of the time, only ESR is used to assess biological inflammatory syndrome in black Africa, as the other acute phase proteins such as CRP are unavailable or too expensive. The autoantibodies (RF and ACPA) are also mostly unavailable [22]. Genetic tests especially the HLA-SE are even less accessible than auto-antibodies. The following paragraphs will be focused on the auto-antibodies.

### 5.1. Rheumatoid Factors

In western countries, the prevalence of RF in RA patients is variable ranging from about 40% to over 60% as shown in Table 3. In black Africa, some studies reported low prevalence of RF in RA patients. In UK, Ravindran *et al.* found similar frequencies of RF among blacks (78%) and whites (72%) recruited in the same rheumatology department of a university hospital in London [68]. Anaya *et al.* reported no significant differences between African Colombians and Mestizo patients in terms of presence of RF which was positive in 14 (78%) African Colombian and 48 (86%) mestizo [13]. The literature underlines a high frequency of RF in healthy African subjects [69]. In Cameroon, Singwe-Ngandeu *et al.* found IgM RF in 16% of healthy subjects [18]. In Nigeria, Greenwood found 11.7% of RF in healthy individuals [14]. Because of their high frequency not only in healthy subjects but also in other autoimmune diseases, the RF are unspecific of RA. That is why new auto-antibodies have been investigated. Thus, it has been demonstrated that ACPA had more specificity than RF for RA diagnosis [70] [71].

### 5.2. Auto-Antibodies against Cyclic Citrullinated Peptide Antibodies

ACPA can be used as diagnostic and prognostic tool. In western countries, the

Table 3. The prevalence of rheumatoid factors in different populations worldwide.

| | Number of participants (n) | RF (%) | Reference number |
|---|---|---|---|
| **Africa** | | | |
| **Low frequency** | | | |
| DRC | 39 | 44.9 | [61] |
| | 72 | 34.7 | [32] |
| Nigeria | 200 | 38.5 | [22] |
| Zimbabwe | 49 | 37.0 | [72] |
| **High frequency** | | | |
| Senegal | 180 | 87.2 | [63] |
| South Africa | 120 | 81.7 | [42] |
| Senegal | 100 | 78.0 | [17] |
| Burkina Faso | 30 | 70.0 | [43] |
| **Western** | | | |
| Syria | 156 | 62.9 | [26] |
| France | 512 | 61.7 | [26] |
| UK | 404 | <42.6 | [29] |
| France | 813 | 42.2 | [62] |
| France | 661 | 44.5 | [66] |

most studied antibodies are anti-CCP2. Their sensitivity for RA diagnosis in Caucasian patients is about 70% (56.9% - 80.4%) [73]. In French population, Dubrous *et al.* showed that anti-CCP Abs test could serve as a better diagnosis marker than rheumatoid factor [74]. Unlike RF that may be undetectable at the beginning of the disease, anti-CCP Abs are present at significant levels at this time and are often detectable long time (over 18 years) before the onset of symptoms [67] [69]. It has been also demonstrated that the detection of anti-CCP Abs in the early stage of the disease is correlated with a more destructive RA [75] [76]. Other involvement of ACPA in the pathogenesis of RA have also been found. Smokers would develop more seropositive RA than those who don't smoke. Patients with seropositive RA are at increased risk of developing ischemic heart disease. It is suggested that the ACPA are produced locally in the joint and are involved in the in situ process of joint destruction [70] [77]. In western countries, other anti-citrullinated antibodies have been studied such as antibodies against Mutated Citrullinated Vimentin (MCV) and anti-CCP3. Data concerning anti-MCV are controversial. In Mexico, Diaz-Toscano *et al.* concluded that adding the assay of anti-MCV antibodies to the determination of anti-CCP2 increases the sensitivity for detecting seropositive RA. Therefore, they proposed the use of both assays in the initial screening of RA [78]. According to an Iranian study, when taken in isolation, the anti-MCV tests have sensitivity and specificity similar to those of anti-CCP and therefore have no value [79]. Other studies have shown that sensitivity and specificity of anti-MCV are lower than those of anti-CCP [80] [81] [82]. In their review, Bartoloni *et al.* reported that anti-MCV can be detectable not only in 15% of healthy subjects, but also in a number of patients with chronic inflammatory and autoimmune disorders and infectious diseases, thereby reducing these antibodies specificity to 65% [83]. ACPA are not pathognomonic of RA. Indeed, Meric de Bellefon *et al.* found in a cohort of 185 patients living with HIV a prevalence of ACPA equal to 10.3%, therefore higher than that of the general population which was 2%. The presence of ACPA was not associated with any joint complaint and 54.05% of the patients were African [84]. This must be taken into account in black Africa where the HIV prevalence remains high.

In black Africa, few studies have been devoted to ACPA. The prevalence of ACPA ranges from 47.2% to 91.4% as shown in **Table 4**. A multicenter cohort study among African Americans conducted by Hughes *et al.* showed that there was a significant association between the HLA-SE and the presence of ACPA. In this study, 86 (48.9%) of 176 patients with ACPA positive RA had at least 1 HLA-SE allele, compared with 36 (32.7%) of 110 patients with ACPA negative RA [35]. The routine use of ACPA is not common in black Africa because of their unavailability or expensiveness. For example, among 250 RA patients under DMARDs in Senegal from 2005 to 2009, ACPA test had been done only for 50 (24.39%) patients [41]. The overall ACPA tests carried in black Africa had used anti-CCP2. No data on anti-MCV have been found in black African patients.

**Table 4.** The prevalence of ACPA in different RA patients worldwide.

| | Number of participants (n) | ACPA (%) | Reference number |
|---|---|---|---|
| **Africa** | | | |
| Senegal | 29 | 91.4 | [63] |
| Senegal | 58 | 90 | [17] |
| South Africa | 120 | 82.5 | [42] |
| Cameroon | 56 | 82 | [18] |
| Burkina Faso | 42 | 81 | [43] |
| DRC | 39 | 51.3 | [61] |
| DRC | 72 | 47.2 | [32] |
| **Western** | | | |
| Netherlands | 566 | 93.4 | [85] |
| Belgium | 86 | 70.9 | [86] |
| Turkey | 176 | 60.2 | [87] |

## 6. Treatment of RA

Because of adverse socio-economic conditions in sub-Saharan Africa, the therapeutic choice depends on local availability, which is limited [41]. It was observed that patients who started DMARDs within 3 months of symptom development showed significantly less radiological progression than those who started treatment later [66]. Unfortunately, in Africa and the Middle East, the initiation of DMARDs in patients with RA is often delayed by ignorance because many practitioners do think about RA only when there is joint damage or positive RF. Thus, the majority of patients had highly active disease at diagnosis. The shortage of rheumatologists also explains the delay in the diagnosis of RA [3] and the misuse of DMARDs. After its institution, treatment with DMARDs is often interrupted for various reasons in black African patients. In Senegal, Ndongo *et al.* reported in 205 RA patients that DMARD treatment was interrupted for at least 5 days per month for 26% of the patients, either because the drugs were out of stock at the local pharmacies and/or because the patients could not afford to purchase them [41]. In developed countries, the success of biological agents has radically improved patient outcomes [88] [89]. Sadly, biological agents are not available in sub-Saharan Africa [41] because of their expensiveness [12] [15] [90] [91] [92]. Ninety-one percent of 56 patients from Cameroon were on DMARDs (especially on methotrexate) but none of them were under biological agent as these drugs are not available in Cameroon [18]. Adverse effects of biological agents and the shortage of rheumatologists are also important difficulties encountered in the management of RA [15]. A degree of caution is warranted before certain DMARDs are prescribed in Africa, as the immunosuppressant properties of the drugs can exacerbate problems associated with endemic infec-

tions such as Tuberculosis, HIV, and malaria [12] [15].

## 7. How to Improve the Management of Rheumatoid Arthritis in Black Africa?

In the light of this review, it seems appropriate to offer solutions to solve the problems that African countries face in the management of RA. All researchers agree that further research with a large cohort size is needed to consolidate understanding of RA in black Africa [3] [12] [15] [16] [22] [50]. In this context, collaboration between western and African research teams must be encouraged. Two major priorities have been identified by Hodkinson *et al.* The most important intervention is training of health care professionals, including family practitioners, primary care nurses, occupational and physiotherapists and orthopedic surgeons, to recognize early inflammatory arthritis and make appropriate referrals to specialists. The second priority would be for rheumatology specialist centers to fast track patients with possible inflammatory arthritis and initiate DMARDs promptly [93] [94]. Pharmaceutical companies might improve access to biological agents by reducing their cost or through schemes similar to the Glivec International Patient Assistance Program (GIPAP) established by Novartis which provides imatinib to chronic myeloid leukaemia patients in the developing world [15]. It is also important that governments include rheumatic diseases in their programs against non-communicable diseases that are currently expanding with the support of WHO [92].

## 8. Key Messages

The studies on RA have increased sharply in black Africa since the first case described in 1959 until the 1990s before experiencing a decline to date. The lack of research funding, partly due to new challenges especially infectious and cardiovascular diseases which governments face may partially explain the decline of interest for RA. The few available studies indicate highly variable results requiring further results to confirm trends. What is clear is that the results obtained in Western patients cannot be directly applied to African black patients. The influence of genetics and environment must be taken into account. Indeed, the expression of HLA-DRB1 genes, the most incriminated gene in susceptibility to RA is not identical between these two types of populations. It is the same for the environmental factors including low consumption of tobacco and the high frequency of endemic infections such as viral and parasitic diseases in African populations. The weakness of data on RA is exacerbated by the challenges of its management. These challenges include the diagnosis and treatment of the disease. There is lack of training including rheumatologists and lack of training of other health workers who are responsible for referring patients to specialists. This results in a delay in diagnosis and consequently delayed treatment, responsible for massive destruction of joints. We must also mention the unavailability or high cost of diagnostic and prognostic tests [95]. These tests include the de-

termination of RF and ACPA, and genetic testing in particular HLA-DRB1 typing. Finally, the lack of financial resources leads to inaccessibility to access conventional DMARDs. In Sub-Saharan Africa countries where biological agents are available, the number of patients who have access hardly exceeds 2% [22].

## 9. Conclusion

The management of RA in black Africa faces many challenges because data on this disease are rare and often contradictory. These data sometimes support the scarcity and benignity of RA in black Africa, but sometimes contradict this hypothesis. The lack of resources and trained health workers is responsible for diagnosis and therapeutic issues such as the unavailability of biological agents and the lack and/or the stock shortage of conventional DMARDs. There is also ignorance and misconceptions in African communities that lead to loss of follow-up. The solutions to these problems not only go through the initiation of larger multicenter studies, but also better training of medical staff. Collaborations between research teams from Western and Africa should be encouraged. Finally, African states should pay particular attention to rheumatic diseases in their programs against non-communicable diseases.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## List of Abbreviations

ACPA or anti-CCP, Anti-Cyclic Citrullinated Peptide Antibodies; CRP, C-Reactive Protein; DAS, Disease Activity Score; DMARDs, Disease-Modifying Anti-Rheumatic Drugs; DRC, Democratic Republic of Congo; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, Erythrocyte Sedimentation Rate; GIPAP, Glivec International Patient Assistance Program; HAART, Highly Active Antiretroviral Therapy; HAQ, Health Assessment Questionnaire; HIV, Human Immunodeficiency Virus; HLA, Human Leukocyte Antigen; Ig, Immunoglobulin; MCV, Mutated Citrullinated Vimentin; RA, Rheumatoid Arthritis; RF, Rheumatoid Factor; SE, Shared Epitope; TB, Tuberculosis; UK, United Kingdom; UN, United Nations; USA, United States of America; WHO, World Health Organization.