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## **Collection and management of selected comorbidities and their risk factors in chronic inflammatory rheumatic diseases in daily practice in France**

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Key words: comorbidities, rheumatoid arthritis, spondyloarthritis, management

## **ABSTRACT (245 words)**

**Background:** In chronic inflammatory rheumatic diseases (CIRDs), comorbidities such as cardiovascular disease and infections are sub-optimally managed. EULAR recently developed points to consider to collect and report comorbidities. The objective of this present study was to develop a pragmatic guide to collect, report and propose management recommendations for comorbidities, from a rheumatologist perspective.

**Methods:** The collection and reporting of comorbidities and risk factors was adapted from the EULAR points to consider. To develop management recommendations, the process comprised (1) systematic literature reviews by 3 fellows and (2) a 2-day consensus process involving 110 experts (rheumatologists and health professionals). Votes of agreement (Likert 1-5 where 5 indicates full agreement) were obtained.

**Results:** The six selected comorbidities were ischemic cardiovascular diseases, malignancies, infections, diverticulitis, osteoporosis and depression. The literature review retrieved 97 articles or websites, mostly developed for the general population. The consensus process led to reporting presence of comorbidities, current treatment, risk factors (e.g. hypertension), screening (e.g. mammography) and prevention (e.g. vaccination). Management recommendations include physical examination (e.g. blood pressure or lymph node examination), prescribing screening procedures, and interpreting results to refer in a timely manner to appropriate other health professionals. Agreement was high (mean±standard deviation, 4.37±0.33).

**Conclusions:** Using an evidence-based approach followed by expert consensus, this initiative furthers the dissemination in France of the EULAR points to consider, and clearly defines what part of the management of comorbidities is potentially within the remit of rheumatologists. This initiative should facilitate systematic management of patients with CIRDs.

## INTRODUCTION

Chronic inflammatory rheumatic diseases (CIRDs) comprise different diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA), and connective tissue disorders. It is known that either CIRDs or their treatments are associated with an increased prevalence or a decreased management of certain comorbidities: thus, cardiovascular diseases and cardiovascular risk factors (such as hypertension or hyperlipidemia),[1-3] infections,[4, 5] depression[6] and osteoporosis [7] are more frequent in patients with CIRDs, whereas there is no demonstrated increase but sub-optimal management compared to the general population of other comorbidities such as malignancies or gastrointestinal diseases.[5, 8] For example, the screening for the detection of breast cancer (a cancer which is not more frequent in CIRDs than in the general population) by mammography may be less frequently performed in women with CIRDs.[9]

Recently, The European League Against Rheumatism (EULAR) developed points to consider for the reporting and collection of comorbidities in CIRDs.[10] In these points, EULAR stipulated that rheumatologists should collect information regarding comorbidities in a standardized way. A pragmatic collection form was developed to collect information relevant to 6 selected comorbidities: ischemic cardiovascular diseases, malignancies, infections, gastrointestinal diseases, osteoporosis and depression.[10] However, EULAR did not give indications on how to manage the comorbidities or risk factors. This was not done for 2 reasons: (a) it is unclear who should be responsible for managing such comorbidities; .[9, 11] and (b) management of comorbidities may be country-specific (e.g. levels of cholesterol necessitating intake of lipid-lowering drugs may vary across countries).[10, 12, 13]

In the present initiative, we aimed to implement the EULAR points to consider for the collection and reporting of comorbidities in a national context (France) and to develop management recommendations for selected comorbidities and risk factors, based on CIRD-specific and general population recommendations, but from a rheumatologist perspective, i.e., taking into account what will be within the rheumatologist's remit and when to refer the patient to other physicians. The final aim was to develop a pragmatic document including both the collection and the management of each comorbidity, for use in clinical practice.

## METHODS

This process included literature reviews and a consensus process in France, in accordance with previous Rencontres d'Experts en Rhumatologie (RER) and 3E (Evidence, Expertise, Exchange) initiatives.[14, 15]

## **Decisions on target population and target comorbidities**

A face-to-face meeting of the steering group took place in March 2015. The group included a convenor (MD), a facilitator (LG), 3 (AB, SD, CD), 10 rheumatologist experts and 3 rheumatology nurses. Three of these were previously involved in the recent EULAR points to consider regarding comorbidities.[10] Based on the EULAR points and on discussions, the target population in terms of patients who should benefit from this initiative, and the list of comorbidities to be considered was developed.

## **Systematic literature reviews**

Systematic literature reviews were performed for each comorbidity. These reviews used the EULAR review as a basis [10] and comprised (a) a complementary review for connective tissue diseases (not formally included in the EULAR review) and (b) a review regarding management of comorbidities in particular by checking the existence of specific recommendations for management including from the French Health authorities (HAS: Haute Autorité de Santé).[16] The objective was to collect published and unpublished recommendations and guidelines for each of the selected comorbidities. This systematic literature review was performed by 3 fellows (AB, SD, CD) from April to September 2015. Detailed information on the process is given in **online supplementary Table 1**.

## **Consensus process**

During a second face-to-face meeting, the steering group developed a draft document dealing with the six groups of comorbidities, and including, for each one, questions to ask for 1) the reporting (*i.e.* occurrence) of the comorbidity; 2) whether screening (*e.g.* mammography) or assessment of risk factors (*e.g.* hypertension and factors for diabetes) had been undertaken; 3) the uptake of any preventive measures (*e.g.* vaccination), and 4) management recommendations. These include prescribing screening procedures, treatment introductions, and/or referrals to appropriate other health professionals.

Then a two-day physical meeting took place in October 2015. Here, 104 physicians and 6 other health professionals (nurses) participated. The comorbidities were split into 3 workshops, each repeated 3 times, every attendee participating at each workshop once. The literature review and the draft document were presented, and the document was adapted according to decisions taken by the group. After the 9 workshops, the 3 versions of each workshop's document were compared by the steering group and a final consensus version was obtained when possible, or 2 alternative versions if consensus could not be reached.

The next day, the consensus versions were presented to the whole group and final decisions were taken by majority voting.

Votes for levels of agreement (Likert 1-5 where 5 indicates full agreement) were obtained from the group for each part of the document.

## RESULTS

### Target population and choice of selected comorbidities

The group considered that this work would be applicable to all patients with CIRDs, including RA, SpA, psoriatic arthritis, connective tissue disorders and would be useful also for patients with vasculitis and potentially multi-site osteoarthritis.

This work focused on 6 selected comorbidities: (1) cardiovascular diseases *i.e.* myocardial infarction, angina, ischemic stroke, transient ischemic attack, heart failure, and peripheral arterial disease, as well as diseases that are also risk factors for ischemic heart disease such as hypertension, diabetes, or dyslipidaemia; (2) malignancies: haematologic, skin, lung, colon, breast, prostate, and uterus; (3) infections: serious, repeated non-serious, tuberculosis, non-tuberculosis opportunistic, as well as vaccinations. Oral hygiene was added; (4) gastrointestinal diseases: gastro-duodenal ulcers and diverticulitis; (5) osteoporosis and (6) depression.

### Systematic literature reviews

A total of 5317 abstracts were retrieved by the searches, of which in the end 64 were included in the final qualitative synthesis, as well as 33 websites/unpublished data (**Table 1**). Of these, 42 were already included in the EULAR systematic literature review [10] (**Table 1**). Most of the available recommendations were recommendations for the general population. From each selected manuscript, the following information was extracted: definition of the comorbidity, how to report its occurrence, proposed screening strategy and proposed screening time interval, and proposed management strategies. All collected data were compiled in tables to help appraisal.

### Consensus for each comorbidity

**Table 2** summarises the points relevant to each comorbidity, also presented in French *in extenso* as **online supplementary Table 2**. There was high agreement within the Task

Force regarding these points (**Table 2**): the mean agreement overall was  $4.37 \pm 0.33$  (1-5 scale).

### **1. Ischemic cardiovascular disease**

Here, the proposed management is in agreement with the recent EULAR recommendations.[17] For total cardiovascular risk estimation, EULAR recommends this assessment for all patients with RA, ankylosing spondylitis or psoriatic arthritis at least once every 5 years and following major changes in anti-rheumatic therapy; [17] the frequency of assessment for each aspect of cardiovascular disease was the object of much discussion.

#### *Hypertension*

Regarding blood pressure, this was felt to be part of usual clinical examination and although no recommendations were found for a proposed frequency, the group recommended blood pressure measurement by the rheumatologist at least once a year (and more frequently if known hypertension, non steroidal drug treatment or in patients with lupus, ie, at every visit).[18, 19] A control then referral is recommended if blood pressure  $\geq 140/90$  mmHg.

#### *Diabetes*

In the general population, the French health authority states glycaemia should be assessed i) every 1-3 years in patients "at risk" according to the FINDRISK score or patients with "at risk" therapy such as glucocorticoids and ii) every year in pre-diabetic patients (ie, if fasting glycaemia is between 1.1 and 1.25 g/l).[20] Here, the consensus was to check for undiagnosed diabetes every 1 to 3 years, thus considering CIRD patients as 'at risk'. The frequency will depend on the presence of risk factors according to FINDRISK including high body mass index, high waist circumference, past hyperglycaemia, family history of diabetes, and glucocorticoid intake.[20] If fasting blood sugar is twice  $\geq 7.0$  mmol/l (1,26 g/l) or if non-fasting blood sugar is  $\geq 11.1$  mmol/l (2 g/l), the recommendation was to refer the patient.

Regarding known diabetes, the group recommended measurement of HbA1c and referral if the target is not attained - the target is usually 7% but depends on age and other health issues).[21-23] Furthermore, weight loss is recommended if high body mass index is detected.

#### *Total cardiovascular risk estimation*

Here, in accordance with current European recommendations, it was decided to assess the Heart-SCORE and to apply a corrective factor of 1.5 in RA (as proposed by European experts), and to perform this assessment at least every 5 years.[17]

Patients with high risk (Heart-SCORE $\geq 5\%$ ) are usually referred to cardiologists.[24] The European recommendations of cardiology state that patients with ultrasonography carotid plaques should be classified at very high risk whatever the Heart-SCORE.[24, 25] Screening

for asymptomatic atherosclerotic plaques by use of carotid ultrasound has been reported to evidence carotid plaques in up to 65% of RA patients at moderate total cardiovascular risk (Heart-SCORE risk 1-5%) thus most patients with moderate risk will be reclassified after carotid ultrasound as very high risk patients.[26] The consensus of this group was that the decision to perform carotid ultrasound, but also the interpretation of this examination and subsequent treatment decisions should be made by a specialist; thus the group proposed to refer all patients with a risk >1% (**Table 2**) though we are aware this will result in frequent referrals.

#### *Dyslipidaemia*

The assessment of dyslipidaemia is recommended in accordance with published EULAR guidelines at least every 5 years and following major changes in anti-rheumatic therapy, ideally when disease activity is stable or in remission.[17]. The target values of LDL cholesterol depend on total cardiovascular risk estimation.[25] Although some rheumatologists prescribe statins, the group consensus was to refer the patient if needed.

#### *Heart failure*

The occurrence of this comorbidity is reported, and symptoms evocative of heart failure lead to referral.[27]

## **2. Malignancies**

Screening for malignancies is useful in the general population.[28-30] The rheumatologist's role includes clinical examination and recommendation or prescription of tests e.g. mammography. In case of any abnormalities, the rheumatologist will refer the patient (**Table 2**).

#### *All cancers*

The group considered that the report of the occurrence of a cancer should be as simple as possible even if other information might be of interest for the treatment decision of a particular patient. Consequently, reporting the date of diagnosis was recommended but treatment received, remission or not, and length of remission were not.

#### *Breast cancer*

A mammography is recommended every 2 years for ages 50-74.[31] In case of family history or personal history of breast cancer, personalized care is needed.

#### *Cervix cancer*

A smear is recommended every 3 years for women between 25 and 65 years old, with sexual activity, after 2 normal smears in the first two years. Controls may be more frequent in lupus patients.[32] If a smear is abnormal (dysplasia, infection, cancer), personalized care is required.[33]

#### *Prostate cancer*

Discrepancies exist between urologists' and oncologists' recommendations.[34-36] The group recommended no systematic screening but a specific visit (to the general practitioner or an urologist) in case of (i) urologic symptoms or (ii) in men older than 45 with either a familial history of prostate cancer (2 or more prostate cancers at any age or 1 or more prostate cancer before 55 years old), or of Afro-Caribbean origin.

#### *Lung cancer*

The group was aware of a specific screening in patients with a smoking history in the United States and in some European countries.[37] However, no systematic screening was recommended due to no existing recommendations in France at this time and due to the absence of specific centres which could do the screening and the follow-up of these patients. The group recommended to report the smoking status and the number of pack-years, and to address smokers to the general practitioner to try to quit smoking.

#### *Lymphoma*

The group recommended lymph nodes palpation every year.

#### *Colorectal cancer*

In the absence of risk factors, it is recommended to screen for colorectal cancer in patients of ages 50-74, every other year (or 5 years after a normal colonoscopy), by a faecal test (either immunochemical test or occult blood test).[38] If a risk factor is present (e.g., personal history of inflammatory bowel disease or of polyps), patients should get a personalized care.

#### *Skin cancer*

The group recommended to visit a dermatologist at least once to assess for skin cancer, then the dermatologist will decide the frequency of these visits.

### **3. Infections**

#### *History of infections*

Tuberculosis, including active tuberculosis and positive tests for tuberculosis should be collected. In case of risk factors, it is proposed to screen for tuberculosis (**Table 2**). [39,40]

Other infections are collected: this includes serious infections (defined as an infection which results in life-threatening, in requiring hospitalization or prolongation of existing hospitalization, or may resulting in persistent or significant disability/incapacity), repeated infections with their localisation, history of viral infections such as human immunodeficiency virus (HIV), hepatitis B or C, zoster, and herpes simplex virus; and opportunistic infections (for which a list is given to help the clinician) (**online supplementary Table 2**).[4,10,40]

Although considering that such collection was critical as it could influence treatment decisions, the group did not propose any specific screening or treatment guidelines, except for tuberculosis; ; but lowest possible doses of glucocorticoids should be used at all times given the links with infections.

### *Predisposing factors for infections*

A visit to the dentist is recommended every year, in view of both the infectious risk represented by poor dental hygiene, and potential links between some CIRDs and periodontitis.[41,42]

The group decided to report the presence of “chronic bronchitis” rather than chronic obstructive pulmonary disease (COPD) because chronic bronchitis is clinically defined (as a cough that occurs every day with sputum production that lasts for at least 3 months, two years in a row), whereas COPD is defined by spirometry parameters. The proposal is to screen for COPD and to refer patients based on a questionnaire (ref) to either a general practitioner or a pneumologist.[43, 44]

Lung fibrosis is mainly an extra-articular manifestation of inflammatory rheumatism such as RA or a side effect of DMARDs [45]. As it is not a comorbidity per se, lung fibrosis was considered beyond the scope of this paper.

### *Vaccinations*

Diphtheria/tetanus/poliomyelitis, influenza and pneumococcus vaccinations are strongly recommended, whereas our suggestions for hepatitis B vaccination and herpes zoster vaccination (Zostavax®) are more informative than prescriptive. [5, 46-49]

Although the risk of herpes zoster is increased in patients treated with TNF inhibitors and Jak inhibitors, we did not give any strong recommendation because i) of a lack of efficacy and safety data in patients with CIRDs, ii) the fact that herpes zoster vaccination is recommended only in the general population after 65 in France and iii) it is a live vaccine and is contraindicated in patients treated with immunosuppressants (**Table 2**). [47-51]

Given the lack of consensus regarding pertussis and measles vaccinations, no recommendations were formulated.[4] Shingles vaccination with Varivax®, a live attenuated vaccine, was discussed but given the limited data available for prevalence of shingles and efficacy of shingles vaccination, the group did not recommend it. [52]

The group decided to record patients declining vaccination as it is a frequent issue in patients with CIRDs.[1]

## **4. Gastrointestinal diseases**

On top of colon/rectum cancer and inflammatory bowel diseases (collected as a risk factor for colon cancer) addressed in the “malignancies” section, the group selected diverticulitis as a comorbidity of interest, mainly because of its increased incidence (0.4% in RA patients) and severity in immunosuppressed patients. [5] When reporting the history of diverticulitis, experts raised the question of possible confusion between diverticulosis and diverticulitis and suggested to check whether patients were hospitalized, received antibiotics or underwent CT

scan. Contrary to the EULAR Task Force [10], we decided not to assess peptic ulcer risk factors because the group felt that peptic ulcer is usually screened for when prescribing symptomatic treatments such as steroids or non steroidal anti inflammatory drugs.

### **5. Osteoporosis**

The history of severe and non-severe osteoporotic fractures is collected. Given that a significant number of osteoporotic vertebral fractures are asymptomatic, the group recommended checking for vertebral fractures using imaging for patients with a height loss of 4 cm or more compared to their height at the age of 20.[5] It was decided not to report a history of osteoporosis (eg through the question : do you have osteoporosis?) as this may lead to over-reporting.[53]

The group proposed to assess bone mineral density by DEXA as recommended for patients at risk of osteoporosis, and also at least once in patients with CIRDs.[54]

The risk of osteoporosis should be assessed by calculation of a score for risk of osteoporotic fracture at 10 years (*i.e.*, FRAX).[55] The group recommended to calculate the FRAX for patients aged 40 or above with bone density T Score >-3 standard deviations, in case of (i) non-severe fracture or (ii) of presence of risk factor(s) .[55] The FRAX interpretation depends on the country and on age; this group recommended to consider anti-osteoporotic treatment if FRAX values were beyond the published intervention levels (**Table 2**).

Although some rheumatologists collect more risk factors than those proposed here, it was considered that for a systematic screening of osteoporosis in patients coming for another motive (eg, a 26 year old male with axial spondyloarthritis) such data collection was sufficient.[9, 54, 55]

Regarding management recommendations, this comorbidity is apart since the specialists for osteoporosis are rheumatologists thus naturally, no referral is recommended. It was decided to not give detailed treatment recommendations within the scope of this project, but rather to refer rheumatologists to current osteoporosis management recommendations.[56]

### **6. Depression**

It is proposed to collect the existence of depression, and as risk factors, a history of depression or anti-depressant drug intake. Recognising the frequency of depression in these patients and its impact, the group proposed to collect the existence of depression / antidepressant drug intake but not perform any extensive screening for depression since such screening has been reported to have conflicting efficacy.[6, 57-59]

## DISCUSSION

Using an evidence-based approach followed by expert consensus, the current work furthers the dissemination and the adaptation to a national context of the EULAR comorbidities initiative and clearly defines what part of the management of comorbidities is potentially within the remit of rheumatologists. The pragmatic document developed should be of use both for annual reviews in hospitals by the rheumatology team, and for private practice rheumatologists in daily practice.

Some comorbidities such as fibromyalgia (or fatigue though this is a symptom) would be important to collect but are missing in this project. However the group anticipated that the screening of a broader scope of comorbidities would make the final process too complex or too extensive to be implemented. Furthermore, this initiative is in accordance with the EULAR initiative.<sup>[10]</sup> Compared to the EULAR comorbidity project, this group added diverticulitis, prostate cancer and herpes zoster vaccination but excluded peptic ulcer since it appeared to the group that the systematic screening of risk factors for peptic ulcer was not useful but rather should be performed in specific cases (eg non steroidal anti inflammatory drug prescription).

The systematic literature review confirmed that specific CIRDS-dedicated recommendations for comorbidities are scarce.<sup>[2,4,40,54]</sup> In most cases, recommendations for the management of comorbidities in CIRDS were extrapolated from those in the general population; Reaching an agreement on what exactly falls within the remit of the rheumatologist was sometimes challenging. Although there is always some personal opinion in consensus processes, we feel the rigorous methodology of the systematic literature reviews and the high number of rheumatologists participating in this consensus exercise are strengths of this project. Furthermore, all these rheumatologists are practicing physicians with clinics, which strengthens the feasibility aspects of such a systematic screening and management programme. Although the work was based on national recommendations, the results are in accordance with other recent EULAR recommendations.<sup>[2,4, 10,40,46,54]</sup> Finally, we consider this project as highly useful to rheumatologists since we propose not only screening and collection questions but also practical management recommendations for each comorbidity, including when and who to refer to other specialists. Thus, this is the first time the exact limits of the rheumatologist role when dealing with comorbidities, has been clearly defined. It is important to note that dealing better with comorbidities should not be seen as replacing high-quality assessment and management of rheumatological conditions – which remain at the heart and core of rheumatology work.

Regarding the management recommendations, some are specific to France as proposed by the national High Authority of Health but many will be applicable across countries. It would be interesting to compare our results with similar initiatives from other countries.

Systematic screenings have been found to be useful for patients, as they draw attention to comorbidities that might otherwise be overlooked.[9,11] The time necessary for this screening raises the question of where it should be optimally performed. Should it be the rheumatologist, perhaps as a dedicated outpatient visit, or a rheumatology nurse e.g. during a systematic yearly review? This project does not answer this question but hopefully encourages a coherent and uniform approach for a review of comorbidities for people with CIRDS and defines the role of the rheumatology team in this regard.

It was difficult to propose precise screening intervals for many of the comorbidities. For total cardiovascular risk estimation, we chose 5 years as proposed by the EULAR task force [17] but for many other comorbidities it was not possible to propose a data-driven optimal interval. However, we believe our proposals will be useful for periodical reviews which might at the minimum be proposed every 5 years (for all comorbidities).

A next step involving patient is now under way, to develop a lay version of the reporting form, i.e., to evaluate in which way patients can self-complete part of the information to facilitate the process. [60]

Dissemination and implementation of recommendations is often an issue. In the present case, it is hoped that the proposed pragmatic form will facilitate this. In any case, further assessment of the feasibility of the document fulfilment and its dissemination will be warranted. In particular, implementation in private practices should be further assessed. Finally, this initiative will necessitate regular updates as some recommendations may change over time such as vaccination patterns or cardiovascular risk assessment.

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**Table 1. Systematic literature review on (a) reporting presence of the comorbidity, treatment for the comorbidity, presence of risk factors for the comorbidity, and previous performance and/or results of screening or prevention procedures; and (b) existing recommendations for management.**

<b>Domain of comorbidities</b>	<b>Number of publications or websites</b>	<b>Number of publications relevant to reporting (how and what to report)</b>	<b>Number of publications relevant to management (how and when to screen and to treat)</b>
Cardiovascular diseases	15	1	14
Malignancies	54	12	54
Infections	12	12	5
Gastrointestinal diseases	1	1	0
Osteoporosis	11	11	5
Depression	4	3	4

**Table 2. Overview of the pragmatic form with (a) collection or not of the different aspects: presence of the comorbidity, treatment for the comorbidity, presence of risk factors for the comorbidity, and previous performance and/or results of screening or prevention procedures; (b) proposed recommendations for management from the rheumatologist's point of view.**

Comorbidity group	Comorbidity	Collection in the form of....				Proposed management by the rheumatologist	Agreement vote, mean (standard deviation)
		Presence of comorbidity	Treatment	Risk factors	Screening or prevention performed		
Cardio-vascular diseases	Hypertension	Yes	Yes	No	Blood pressure measure	Perform blood pressure measure: once a year for all, at every visit for lupus patients: referral if abnormal values	4.82 (0.45)
	Diabetes	Yes	Yes	Obesity, high waist circumference, family history of diabetes, glucocorticoids	Fasting blood sugar Body mass index calculation HbA1c if diabetes	Assess fasting blood sugar every 1-3 years: referral if abnormal values Weight loss counselling if overweight HbA1c every 3-6 months if known diabetes: referral if abnormal values	4.36 (0.93)
	Total cardiovascular risk estimation	Yes (high and very high risk situations)	Yes (anti-agregants/ anti-coagulants)	Heart-SCORE components	Heart-SCORE calculation	Calculation of heart-SCORE at least every 5 years and following major changes in anti-rheumatic therapy. Referral to cardiologist if Heart-SCORE >1%	4.31 (0.81)
	Hyperlipidemia	Through treatment	Yes	No	LDL-cholesterol assessment	Assess LDL-cholesterol at least every 5 years or following major changes in anti-rheumatic therapy. tocompare to target defined according to total cardiovascular risk estimation. Referral if target not reached.	4.44 (0.68)

	Heart failure	Yes	No	No	Symptoms at clinical examination	Referral if symptoms	4.46 (0.72)
Malignancies	Breast cancer	Yes	No	Family history	Mammography	Recommend/prescribe mammography every 2 years for age 50-75. If risk factors, referral.	4.56 (0.69)
	Cervix cancer	Yes	No	No	Cervical smear Human Papilloma Virus (HPV) vaccination	Recommend/prescribe cervical smear every 3 years for age 25-65 if sexual activity, if 2 smears one year apart are normal If abnormal smear, referral. Recommend HPV vaccination for girls age 11-14 years.	4.62 (0.69)
	Prostate cancer	Yes	No	Yes (symptoms or family history or ethnic risk – Afro-Caribbean origin)	No	If risk factors, referral	4.50 (0.77)
	Lung cancer	Yes	No	Yes (smoking)	No	If smoking, recommend referral to encourage interruption	3.90 (1.21)
	Lymphoma	Yes	No	No	Adenopathy clinical examination	Perform adenopathy clinical examination once a year	4.30 (1.15)
	Colorectal cancer	Yes	No	Yes (inflammatory bowel disease, polyps, family history)	Faecal immunochemical test or faecal occult blood test Colonoscopy	Recommend/prescribe faecal blood test every 2 years if age 50-74 If risk factors, referral	4.41 (0.93)
	Skin cancer	Yes	No	No	Clinical examination by dermatologist	Refer for clinical examination by dermatologist at least once in lifetime	4.00 (1.25)
Infections	Tuberculosis	Yes (active disease or just positivity of screening tests)	Yes (treatment if tuberculosis)	Yes (social status, drug use, contact with tuberculosis)	Vaccination status	Screen for tuberculosis if risk factors	3.78 (1.31)

	Serious infections	Yes and only one or more	No	No	No	Recommend awareness and consider treatment modification	3.79 (1.46)	
	Repeated infections	Yes and type						
	Opportunistic infections	Yes, only one or more, and type (with list)						
	Viral infections	Yes and type					4.60 (0.74)	
	Dental status	No	No	No	Visit to dentist and date	Recommend visit to dentist once a year	4.65 (0.75)	
	Chronic bronchitis	Yes	No	Yes (age>40, smoking, cough, dyspnea)	No	If 3 signs out of 4 are present, referral	4.15 (1.18)	
	Vaccine-preventable infections	No	No	No	Vaccination status for diphtheria, tetanus, poliomyelitis	Recommend vaccination every 10 years (if biologic treatment) to every 20 years	4.93 (0.43)	
					Vaccination status for influenza	Recommend vaccination against influenza every year if immunosuppressants or age>65	4.82 (0.58)	
					Vaccination status for pneumococcus	Recommend vaccination against pneumococcus if immunosuppressants (to be repeated dependent on vaccination scheme)	4.79 (0.58)	
					Yes for hepatitis B	Vaccination status for hepatitis B	Propose hepatitis B vaccination before a biologic prescription, especially if presence of risk factors	4.40 (0.92)
					No	Vaccination status for herpes zoster	Inform that herpes zoster vaccination is recommended after 65, no recommendation in CIRDS, and contraindication if immunosuppressants including methotrexate and glucocorticoids	4.03 (1.27)

						(live vaccine)	
Gastrointestinal diseases	Diverticulitis	Yes	No	No	No	If present take into account when prescribing glucocorticoids/NSAIDs.	4.53 (0.98)
Osteoporosis	Fractures	Yes	No	See below	Height loss>4 cm	Prescription of treatment if major osteoporotic fracture Prescription of spine radiographs if height loss> 4 cm	4.63 (0.61)
	Osteoporosis risk factors	No	No	See below	Bone mineral density result	Prescription of bone mineral density (a) in the general population if presence of risk factors for osteoporosis, (b) in menopausal women if presence of risk factors, (c) in patients with CIRDs at least once in lifetime	4.30 (0.86)
		No	No	Yes (components of FRAX score)	FRAX calculation	Calculation of FRAX score if age >40, T Score >-3 Standard Deviations and either non major osteoporotic fracture OR risk factors.  Consider treatment if values above threshold.	4.00 (1.35)
Depression	Depression	Yes	No	Yes (history of depression or of anti-depressant treatment)	No	None	3.90 (1.52)

**Online supplementary Table 1. Literature review methods to collect information on comorbidity management in CIRDs**

Domains	Cardiovascular diseases	Infections	Cancers	Gastro-intestinal diseases	Osteoporosis	Depression
Key words for search in PubMed Medline in July 2015	((("Arthritis, Psoriatic"[Mesh] OR "Arthritis, Rheumatoid"[Mesh] OR "Spondylarthritis"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh] OR "Spondylitis, Ankylosing"[Mesh] OR "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis"[Mesh]) AND ("Cardiovascular Diseases"[Majr] OR "Cardiovascular System"[Majr] OR "Myocardial Infarction"[Mesh] OR "Heart Failure"[Mesh] OR "Peripheral Arterial Disease"[Mesh])) OR cardiovascular risk OR "Dyslipidemias"[Majr] OR "Hypertension"[Majr])	infection/diagnosis / OR "infection prevention/ (Guideline[ptyp] OR Practice Guideline[ptyp])	((arthritis[MeSH Terms] OR rheumatic disease/complications[MeSH Terms]) OR (lupus erythematosus disseminatus[MeSH Terms] OR (Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis[MeSH Terms] ) AND (Guideline[ptyp] OR Practice Guideline[ptyp]) AND (neoplasms[MeSH Terms] OR (Guideline[ptyp] OR Practice Guideline[ptyp]) AND (neoplasms[MeSH Terms]))	("Diverticulitis"[Mesh] AND (Guideline[ptyp] OR Practice Guideline[ptyp]))	"exp osteoporosis/ (Guideline[ptyp] OR Practice Guideline[ptyp])	((arthritis[MeSH Terms] OR rheumatic disease/complications[MeSH Terms]) OR (lupus erythematosus disseminatus[MeSH Terms] OR (Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis[MeSH Terms] ) AND (Guideline[ptyp] OR Practice Guideline[ptyp]) AND (depression[MeSH Terms] OR (Guideline[ptyp] OR Practice Guideline[ptyp]) AND (depression[MeSH Terms]))

	] OR "Diabetes Mellitus"[Majr] OR "Heart Failure"[Majr] OR "Peripheral Arterial Disease"[Majr])) AND ("Guideline"[Publication Type] OR "Guidelines as Topic"[Mesh] OR "Practice Guideline"[Publication Type] OR "Health Planning Guidelines"[Mesh])					
Number of abstracts	555	496	3793	4	312	157
Number of published articles selected	8	12	28	1	11	4
Number of French specific recommendations on websites but not in PubMed	5	6	26	1	5	0
Number of other websites/other unpublished data	2 congress abstracts	0	0	0	0	0
Total number of references analysed,	15	12	54	1	11	4

including articles websites							
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