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ORIGINAL ARTICLE

Is Routine Viral Screening Useful in Patients With Recent-Onset Polyarthritis of a Duration of at Least 6 Weeks? Results From a Nationwide Longitudinal Prospective Cohort Study

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Objective. **To study the contribution of routine viral screening tests in patients with early rheumatoid arthritis (RA) or a potential for progressing to RA.**

Methods. **Eight hundred thirteen patients with swelling of at least 2 joints for at least 6 weeks and a symptom duration of less than 6 months in the ESPOIR cohort were screened for parvovirus B19 (IgG and IgM anti–parvovirus B19 antibodies), hepatitis B virus (HBV; hepatitis B surface antigen), hepatitis C virus (HCV; anti-HCV antibodies), and human immunodeficiency virus (HIV; anti–HIV-1 and -2 antibodies).**

Results. **Parvovirus B19 testing was performed in 806 patients and showed longstanding immunity in 574 (71.2%) and no antibodies in 223 (27.7%). Among the 9 remaining patients (7 IgG positive/IgM positive, 1 IgG negative/IgM positive, and 1 IgG indeterminate/IgM positive), only 2 (0.25%; 95% confidence interval [95% CI] 0–0.99%) had a positive polymerase chain reaction test for parvovirus B19; these patients (women ages 34 and 40 years) had no extraarticular signs. HIV seroprevalence was 0.12% (n = 1 of 813; 95% CI 0.01–0.8%) and HCV seroprevalence was 0.86% (n = 7 of 808, 95% CI 0.38–1.86%). HCV-related arthritis was diagnosed in 4 patients (0.5%). HCV-seropositive patients had significantly higher transaminase levels than the other patients ($P = 0.001$), with no significant differences for the other laboratory data. HBV seroprevalence was 0.12% (n = 1 of 808; 95% CI 0.01–0.8%); the positive HBV status was known before study inclusion, and the patient had no diagnosis of HBV-related arthritis. Finally, routine viral testing identified 2 patients with parvovirus B19 infection and 3 with HBV infection (0.6%; 95% CI 0.2–1.5%). Cost was €85.05 per patient (total €68,720).**

Conclusion. **Routine serologic testing did not contribute substantially to the diagnosis in this context.**

INTRODUCTION

The appropriateness of routine screening tests for viral infections in patients with recent-onset polyarthritis is a matter of debate. Such tests might assist in the diagnosis of polyarthritis suggesting rheumatoid arthritis (RA) for 3 reasons (1–4). First, like most autoimmune diseases, RA may originate in a viral infection. Evidence supporting a role for viruses includes results from animal models, epidemiologic data showing temporal and spatial associations, and the detection of viral material in tissues. The many pathophysiologic hypotheses involve molecular mimicry, epitope spreading, bystander activation, dual receiver, and viral "déjà vu." Second, viral infections can mimic early joint disease, including early RA. In France, in patients with polyarthritis of a duration of at least 6 weeks, only 4 viruses are potentially associated with arthritis:

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Significance & Innovations

- Routine serologic testing did not contribute substantially to the diagnosis in patients with swelling of at least 2 joints for at least 6 weeks and a symptom duration of less than 6 months.
- Nevertheless, there remains a need to exclude hepatitis B virus, hepatitis C virus, and human immunodeficiency virus in selected high-risk individuals for testing in this context and/or prior to immunosuppression.

hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and parvovirus B19. The diagnosis of viral arthritis rests on the occurrence of acute polyarthritis during an outbreak of viral illness and/or with suggestive concomitant signs. Third, the immunosuppressive agents used to treat RA can worsen viral infections, which must therefore be diagnosed before treatment initiation.

The likelihood of identifying the cause of recent-onset polyarthritis may depend on the combination of clinical, imaging, and laboratory tests used. However, the diagnostic efficacy of the many possible test combinations has not been determined. There are no scientific data for developing a consensus on this point. Consequently, there may be substantial variation among rheumatologists regarding the tests used to evaluate recent-onset polyarthritis.

We previously evaluated the prevalence of HBV and HCV in the ESPOIR cohort of patients with possible RA (5). Here, our objective was to study the contribution of routine serologic tests for the 4 viruses potentially associated with arthritis in European countries in patients with recent-onset polyarthritis of a duration of at least 6 weeks.

MATERIALS AND METHODS

Study population. The French Society for Rheumatology constituted a nationwide longitudinal prospective cohort, known as the ESPOIR cohort (6), to enable investigations of the diagnosis, outcome markers, epidemiology, pathogenesis, and medicoeconomics of early arthritis and RA. The cohort was established by asking general practitioners and rheumatologists to refer patients with recent-onset arthritis to hospitals participating in the ESPOIR project. Patients were eligible for inclusion in the cohort if they had a definitive or probable clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with a potential for progressing to RA.

Patients were included if they met the following criteria: age >18 and <70 years, swelling of at least 2 joints for at least 6 weeks, symptom duration of less than 6 months, and no prior treatment with disease-modifying antirheumatic drugs or glucocorticoids; however, patients who took glucocorticoids for no longer than 2 weeks, in a mean dosage of no greater than 20 mg/day, and who stopped this treatment at least 2 weeks earlier could be included. Included patients were evaluated every 6 months for 2 years and then once a year.

The Institutional Review Board of the center coordinating this nationwide study (Montpellier University Hospital) approved the study. Prior to inclusion, all patients gave their written informed consent to participate in this study.

Study design. For the prospective longitudinal ESPOIR cohort study, the baseline assessment included a standardized interview; a general physical examination; laboratory tests (standard blood and urine parameters; enzyme-linked immunosorbent assay [ELISA] for IgM, IgG, and IgA rheumatoid factors; tests for anti–cyclic citrullinated peptide [anti-CCP] and antinuclear antibodies; and HLA–DR phenotype determination); and radiographs of the chest, pelvis, hands, and feet in the posteroanterior view and of the feet in the oblique view. Each patient was asked to undergo an evaluation by an office-based rheumatologist every 6 months for 2 years and once a year thereafter. These evaluations were free of charge. Part of the serum sample collected at baseline was stored for further laboratory tests.

Serologic tests. As previously published (5), tests for hepatitis B surface antigen (HBsAg) and anti-HCV antibody were performed on 500 μl of the stored serum sample of each patient. All serologic tests were done at the microbiology laboratory of the Brest Teaching Hospital, Brest, France, by a single microbiologist (VN). HBsAg was detected using a chemiluminescent microparticle immunoassay (CMIA; Architect HBsAg assay). When the test was positive, a second sample of the stored blood was tested in the same way. If this second test was also positive, a neutralization test was performed to confirm the result. Patients with positive confirmation tests were classified as HBsAg positive.

Anti-HCV antibodies were detected using a CMIA (Architect anti-HCV assay). Positive samples were tested using a confirmation immunoblot test (recomBlot HCV IgG 2.0, Microgen, and INNO-LIA HCV). Patients with positive confirmation tests were classified as anti-HCV positive.

Antibodies to HIV-1 and HIV-2 antibodies were detected using a CMIA. Positive samples were tested using Western blotting. Patients with positive Western blots were classified as HIV positive.

IgG and IgM antibodies to parvovirus B19 were detected using ELISA. The index (patient value/cutoff) was considered negative if lower than 0.9, indeterminate if between 0.9 and 1.1, and positive if greater than 1.1. IgM-positive samples were tested using a polymerase chain reaction (PCR) assay. Patients with positive PCR results were classified as definitive parvovirus B19 infection. IgM-positive samples were classified as possible parvovirus B19 infection.

Statistical analysis. Data were keyboarded and then analyzed using the Statistical Package for the Social Sciences, version 15.0 (SPSS). The chi-square test (or Fisher's exact test, where appropriate) and the Mann-Whitney test

Table 1. Baseline characteristics of the 813 patients in the ESPOIR cohort*

	Value
Women/men, no.	624/189
Age, mean ± SD years	48 ± 12.5
Disease duration, mean ± SD days	103 ± 52
Swollen joint count, mean ± SD	7.2 ± 5.4
Tender joint count, mean ± SD	8.4 ± 7
DAS28, mean ± SD	5.1 ± 1.3
ESR, mean ± SD mm/hour	29.5 ± 24.5
Elevated CRP level, no. (%)	316 (38.9)
IgM-RF, no. (%)	359 (44.2)
ACPAs, no. (%)	315 (38.7)
ACR criteria for RA met, no. (%)	578 (71.3)

* DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IgM-RF = IgM rheumatoid factor; ACPAs = anti–citrullinated peptide antibodies; ACR = American College of Rheumatology; RA = rheumatoid arthritis.

were used. *P* values less than 0.05 were considered significant.

RESULTS

Patient characteristics. The main characteristics of the 813 patients included in the ESPOIR cohort are listed in Table 1.

Tests for antibodies to parvovirus B19. Of the 806 tested patients, 574 (71.2%) had ELISA results indicating longstanding immunity (IgG positive/IgM negative) (Figure 1). The 2 IgG-positive/IgM-indeterminate patients were classified as having longstanding immunity (6). No IgG or IgM antibodies were found by ELISA in 186 patients; in addition, 3 IgG-negative/IgM-indeterminate patients and 34 IgG- indeterminate/IgM-negative patients were classified as nonimmune based on the reasons given above. Therefore, 223 patients (27.7%) were not immune. Of the remaining 9 patients (1.1%; IgG positive/IgM positive, n = 7; IgG negative/IgM positive, n = 1; and IgG indeterminate/IgM positive, n = 1), 2 had a positive PCR test for parvovirus B19. Of the 7 IgG-positive/IgM-positive patients, 2 had a positive PCR test for parvovirus B19. Among the 5 remaining patients (IgG positive/IgM positive/PCR negative), 3 had another diagnosis than parvovirus infection (1 Sharp syndrome, 1 spondylarthropathy, and 1 RA) after a 2-year followup. The IgG-negative/IgM-positive patient had HCV and the IgG-indeterminate/IgM-positive patient was considered as having RA after a 2-year followup.

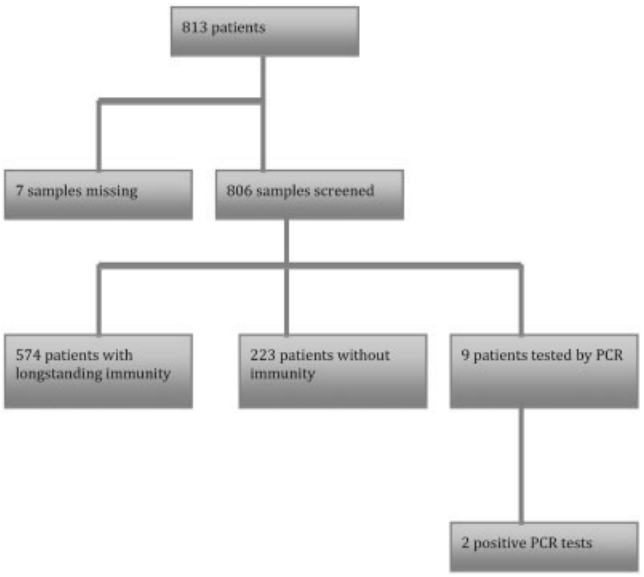

Figure 1. Screening for parvovirus B19. PCR = polymerase chain reaction.

Table 2. Characteristics of the 2 patients with positive polymerase chain reaction tests for parvovirus B19 at inclusion*

	Patient 1	Patient 2
Sex	Female	Female
Age, years	40	34
Morning stiffness, minutes	1,440	0
Asthenia (VAS/100)	47	45
Tender joint count at rest/44	31	35
Tender joint count on mobilization/44	43	59
Swollen joint count/28	16	4
Positive serum rheumatoid factor and ACPAs	No	No
Radiographic erosions	No	No
Certainty of RA diagnostic (VAS/100)	71	50
Possible RA	Yes	Yes
Other diagnoses suggested	Sjögren's syndrome	SLE/Sjögren's syndrome

* VAS = visual analog scale score; ACPAs = anti–citrullinated peptide antibodies; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Therefore, the prevalence of parvovirus B19–definitive infection among these patients was 0.25% (n = 2; 95% confidence interval [95% CI] 0–0.99%). We cannot exclude parvovirus infection in the 2 patients without any diagnosis after a 2-year followup. Parvovirus infection was considered as improbable in patients with another diagnosis at this time.

Both patients with PCR tests positive for parvovirus B19 were women (Table 2). They were ages 34 and 40 years. Both were free of extraarticular signs and were classified as having undifferentiated connective tissue disease (possible Sjögren's syndrome). After 4 years, they had no synovitis, they had no erosions, their tests for rheumatoid factors were negative, and they were not taking disease-modifying antirheumatic drugs.

Tests for hepatitis viruses. The HBV test results have been published in part elsewhere (4). HBV tests were done in 808 patients (Figure 2).

The CMIA for anti-HCV antibodies was positive in 16 (1.98%) of the 808 patients. Of these 16 patients, 7 of 808

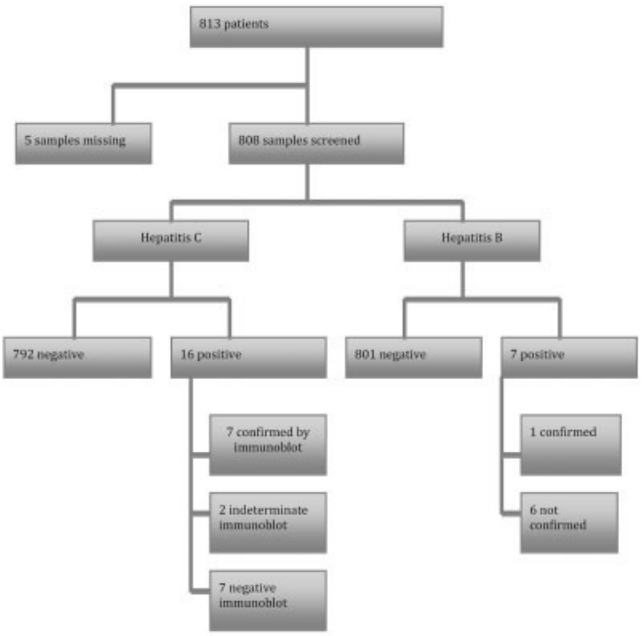

Figure 2. Screening for hepatitis B and hepatitis C.

(0.86%; 95% CI 0.38–1.86%) had negative results and 2 had indeterminate results from the immunoblotting test. The 2 patients with indeterminate immunoblots underwent blood collection at their study centers for further anti-HCV tests, which were negative. Of the 7 patients with positive CMIA and immunoblot results, 4 of 808 had a diagnosis of HCV-related arthritis (0.50%; 95% CI 0.16–1.4%). Compared to the overall population, the 7 HCV-positive patients had significantly higher serum transaminase levels (alanine aminotransferase [ALT], 41.5 IU versus 23.2 IU, $P = 0.02$; and aspartate aminotransferase [AST], 39.2 IU versus 21.83 IU, $P = 0.001$); however, only 2 HCV-positive patients had AST or ALT levels greater than 40 IU (upper limit of normal for aminotransferases <40). No other significant differences were found for any of the study variables, including the erythrocyte sedimentation rate, C-reactive protein level, or presence of anti-CCP antibodies. The proportion of HCV-positive patients was significantly larger in the subgroup with a history of blood transfusions than in the other patients (3.7% versus 0.42%; $P = 0.02$). Of the 7 HCV-positive patients, 4 were known carriers of anti-HCV antibodies before study inclusion and 2 were born in areas where the prevalence of viral hepatitis is high (Togo and Vietnam).

Of the 808 patients tested, 7 (0.86%) had positive CMIA results for the HBsAg, of whom 1 of 808 had a positive confirmation test (0.12%; 95% CI 0.006–0.8%). In the remaining 6 patients, the serum samples were inadequate for confirmation testing. None of the 7 patients had been given a diagnosis of HBV-related arthritis. The patient with a positive confirmation test was known to be HBsAg positive at study inclusion.

Tests for HIV antibody. HIV testing was performed in all 813 patients. The CMIA for anti-HIV antibodies was positive in a single patient, yielding a seroprevalence of 0.12% (95% CI 0.01–0.8%). The HIV-positive patient was known to be infected with HIV before study inclusion and had not been given a diagnosis of HIV-related arthritis.

Usefulness of routine viral serologic testing. Routine serologic testing ensured the detection of 2 patients with parvovirus B19 infection and 3 patients with HCV infection. Therefore, among the 813 patients, 5 (0.6%; 95% CI 0.2–1.5%) had viral infections detected (Table 3). The cost per patient of serologic screening (without confirmation tests) was €32.40, €17.55, €18.90, and €16.20 for parvovirus B19, HBV, HCV, and HIV, respectively. The total cost was €68,720 (€85.05 per patient).

DISCUSSION

The seroprevalences of HCV, HBV, HIV, and parvovirus B19 infection in the ESPOIR cohort were 0.86%, 0.12%, 0.25%, and 0.12%, respectively.

A cross-sectional survey of the prevalence of HBV and HCV infections was conducted in 2004 among 14,416 residents of metropolitan France ages 18–80 years (7). Weighted estimates were computed. The overall prevalence of anti-HCV antibodies was 0.84% (95% CI 0.65–1.10%). Among anti-HCV–positive individuals, 57% (95% CI 43–71%) knew their serologic status before the survey and 65% (95% CI 50–78%) were positive for HCV RNA. The prevalence of HBsAg was 0.65% (95% CI 0.45–0.93%). Parvovirus B19 infection is common (8). The prevalence of antibodies to parvovirus B19 was 50% to 60% among adults ages 16–40 years and greater than 85% in those ages >70 years. Therefore, the seroprevalence rises

Table 3. Results of routine screening for parvovirus B19, hepatitis B, hepatitis C, and HIV in the ESPOIR cohort*

	Total	Previously known	Detected
Parvovirus B19, no./total (%)	2/806 (0.25)	0	2/806 (0.25)
Hepatitis B, no./total (%)	1/808 (0.12)	1/808 (0.12)	0
Hepatitis C, no./total (%)	7/808 (0.87)	4/808 (0.5)	3/808 (0.37)
HIV, no./total (%)	1/813 (0.12)	1/813 (0.12)	0/813 (0)
Total no.	11	6	5
Total % (95% CI)	1.36 (0.72–2.5)	0.74 (0.3–1.7)	0.6 (0.2–1.5)

* HIV = human immunodeficiency virus; 95% CI = 95% confidence interval.

after 40 years of age, suggesting continued exposure to the virus. In France, the prevalence of HIV infection is 0.4%. The number of new cases diagnosed each year between 2003 and 2008 in France is estimated at 6,500 to 7,600. Thus, the seroprevalences in our study were similar to those seen in the general population in France (7–9). They are also consistent with a previous study evaluating the usefulness of routine serologic testing in 322 patients with inflammatory polyarthralgia, monarthritis, oligoarthritis, or polyarthritis of a duration of less than 1 year (10).

Like most autoimmune diseases, RA may be of viral origin. The pathogenesis of virus-associated arthritis is poorly understood. The disease is believed to develop as the result of several non–mutually exclusive mechanisms, including direct viral infection and induction or amplification of autoimmunity by the virus. Viruses can induce autoimmunity and inflammation via numerous mechanisms such as molecular mimicry, bystander activation, and epitope spreading (11). However, our results provide evidence against a major role for viral infection in the pathogenesis of RA, as the seroprevalences were similar to those seen in the general population.

Polyarticular disease is common after primary parvovirus B19 infection, especially in adults (60%). The presentation may suggest RA, particularly as women are predominantly affected and multiple autoantibodies (e.g., rheumatoid factors, antinuclear antibodies, and anti–double-stranded DNA antibodies) may be produced (8,12,13). Parvovirus B19 is known to cause erythema infectiosum, arthralgia, aplastic crisis in patients with red cell defects, and chronic anemia in immunocompromised patients. The diagnosis relies on serologic and PCR tests. PCR test results must be interpreted with caution, as false-positives are common. IgM antibodies are detectable starting on day 7 after exposure and for up to 6 months. Their presence is suggestive but not necessarily diagnostic. Parvovirus B19 serologic testing can assist in the differential diagnosis, thereby avoiding the use of unnecessary medications, as parvovirus B19–related arthritis requires only symptomatic treatment. In addition, a positive test is likely to reassure the patient regarding the prognosis. However, in the absence of PCR confirmation, routine serologic testing would lead to overdiagnosis of parvovirus B19 infection, as the false-positive rate is high. In our study, of 9 seropositive patients, only 2 had positive PCR tests. Among the 7 remaining patients, a diagnosis of parvovirus seems improbable in 5 for whom another diagnosis has been made, but we cannot conclude for 2.

Immunoblotting was positive for HCV infection in 7 patients (previously known in 4) and for HBV infection in 1 patient (previously known). Using the CMIA without confirmation by immunoblotting would have resulted in overdiagnosis related to false-positive results. Although the 7 HCV-positive patients had significantly higher serum transaminase levels than the overall population, only 2 HCV-positive patients had AST or ALT levels greater than 40 IU, and thus that is not a reliable strategy to screen for HCV only if elevated transaminase is present. No other significant differences were found for any of the study variables. Therefore, HBV and HCV tests may be best reserved for patients with risk factors for viral hepatitis, suggestive symptoms, high liver enzyme levels, a history of hepatitis, or a history of living in high-prevalence areas (5). HIV serologic tests should also be performed selectively in those patients with risk factors (high prevalence areas, behavior at risk for sexually transmitted diseases, or prior blood transfusion) (14).

Therefore, few patients in the ESPOIR cohort had RA-like polyarthritis due to a viral infection. In most cases of virus-associated arthritis, the diagnosis is aided by an ongoing outbreak of viral illness, extraarticular manifestations, or suggestive laboratory findings. Routine serologic testing results in overdiagnosis due to false-positive results, unless confirmation testing is performed. Moreover, routine serologic testing is costly (€85.50 per patient in our study) (15). However, HBV and HCV serologic tests must be performed routinely before initiating methotrexate (16–18) or biotherapeutic agents (19).

HIV serologic testing is mandatory before initiating biologic agents (19). Few data are available regarding the impact of immunosuppressive agents in patients with parvovirus B19 infection. A few cases of bone marrow failure have been reported (20–22). After 24 months, 375 of 808 ESPOIR cohort patients had received methotrexate and/or biologic agents. Thus, a substantial proportion of patients with recent-onset polyarthritis require viral serologic testing at some point. However, most patients with recent-onset polyarthritis do not require immunosuppressive agents or receive such agents only after some considerable time. The very low seroprevalences found in our study suggest that viral serologic tests may be best performed as part of the evaluation done before starting immunosuppressive therapy, rather than routinely at baseline. This last point remains controversial, however. A recent practice survey in France (23) showed that serologic HCV testing was deemed advisable by 19% of rheumatologists for patients with possible RA and 9% for patients with probable RA; corresponding figures for HBV testing were 18% and 8%, respectively. For patients with possible RA, 8% of the rheumatologists screened for parvovirus B19 and 11% screened for HIV.

In conclusion, the seroprevalences of HBV, HCV, HIV, and parvovirus B19 in our population of patients with recent-onset polyarthritis suggesting RA were not increased compared to the general population. Routine serologic testing did not contribute substantially to the diagnosis of recent-onset polyarthritis (2 parvovirus B19 infections and 3 HCV infections were newly diagnosed; 1 HBV and 4 HCV infections were known previously) and carries a risk of overdiagnosis due to false-positive results. However, serologic testing might avoid the use of inefficient and potentially harmful treatments in a small number of patients wrongly believed to have RA. HIV, HBV, and HCV serologic tests must be performed before initiating immunosuppressive or hepatotoxic drugs. Screening of high-risk patients is probably more effective than routine screening.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saraux had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data. Varache, Narbonne, Dougados, Saraux.

ROLE OF THE STUDY SPONSOR

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