Responder Interferon λ Genotypes Are Associated With Higher Risk of Liver Fibrosis in HIV–Hepatitis C Virus Coinfection

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Background. Liver fibrosis progresses faster in individuals coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Interferon λ3 (IFN-λ3) has both antiviral and proinflammatory properties. Genotypes at IFNL single-nucleotide proteins (SNPs; rs12979860CC and rs8099917TT) are linked to higher HCV clearance, potentially via rs8103142. We examined the relationship between IFN-λ genotypes and significant liver fibrosis in HIV–HCV coinfection.

Methods. From the prospective Canadian Co-infection Cohort (n = 1423), HCV RNA–positive participants in whom IFN-λ genotypes were detected and who were free of fibrosis, end-stage liver disease, and chronic hepatitis B at baseline (n = 485) were included. Time to significant fibrosis (defined as an aspartate transaminase level to platelet count ratio index [APRI] of ≥1.5) by IFN-λ genotypes was analyzed using Cox proportional hazards, with adjustment for age, sex, ethnicity, alcohol use, CD4+ T-cell count, HCV genotype, γ-glutamyl transferase level, and baseline APRI. Haplotype analysis was performed, with adjustment for ethnicity.

Results. A total of 125 participants developed fibrosis over 1595 person-years (7.84 cases/100 person-years; 95% confidence interval [CI], 6.58–9.34 cases/100 person-years). Each genotype was associated with an increased fibrosis risk, with adjusted hazard ratios of 1.37 (95% CI, .94–2.02) for rs12979860CC, 1.34 (95% CI, .91–1.97) for rs8099917TT, and 1.79 (95% CI, 1.24–2.57) for rs8099917TT. Haplotype TCT was also linked with a higher risk (hazard ratio, 1.14 [95% CI, .73–1.77]).

Conclusions. IFN-λ SNPs rs12979860, rs8099917, and rs8013142 were individually linked to higher rates of fibrosis in individuals with HIV–HCV coinfection. IFN-λ genotypes may be useful to target HCV treatments to people who are at higher risk of liver disease.

Keywords. liver fibrosis; IFNL; HIV–HCV co-infection.

Despite the availability of effective treatment for and control of human immunodeficiency virus (HIV) infection, liver disease is especially serious in individuals with hepatitis C virus (HCV) and HIV coinfection. In coinfected individuals, liver fibrosis progression is accelerated, leading to cirrhosis, hepatocellular carcinoma, or end-stage liver disease [1]. While curing HCV is now increasingly possible with the latest direct-acting antiviral agents, treatment uptake remains low, and costs are high. HCV reinfection after cure remains a real problem among active injection-drug users, as well as among men who have sex with men, who make up the majority of the coinfected population in Canada. Furthermore, even with HCV infection cure, advanced cirrhosis can be irreversible, and other risks associated with hepatocellular carcinoma and portal hypertension remain [2]. Because the risk of liver disease is higher in coinfected individuals, identifying etiologic determinants in this group is especially pressing, as it can enable better screening and treatment decision-making.

Among host genetic factors that could potentially affect liver fibrosis progression are the single-nucleotide polymorphisms (SNPs) around the interferon λ3 (IFN-λ3) gene (IFNL3; formerly referred to as IL28B). In several studies, these SNPs (rs12979860 and rs8099917) were strongly predictive of favorable HCV treatment response and spontaneous clearance in both monoinfected [3, 4] and coinfected [5, 6] populations. The odds of spontaneous clearance or favorable treatment response were >3 times higher in those inheriting 2 copies of the responder alleles as compared to those with 1 or 0 copies. IFN-λ3 genotypes are also predictive of treatment responses with direct-acting antiviral agents, although the association is weaker [7].

Reports on the relationship between IFN-λ genotypes and fibrosis progression are contradictory, owing to heterogeneity in study designs, measurement of outcomes, and study populations. Some postulate no relationship [8], whereas others found,
Interestingly, a more rapid progression to fibrosis and cirrhosis in those with the responder genotype (that is, the genotype linked with spontaneous clearance and improved treatment response) [9, 10]. Conversely, other studies found a greater risk of severe fibrosis [11] associated with the nonresponder genotype.

Given the role of inflammation in liver fibrosis progression, the high inflammation that persists in coinfected individuals despite HIV treatment [1], as well as evidence that IFN-λ SNPs are linked with proinflammatory immune responses, it is possible that IFN responses play a role in the natural history of HCV infection and can affect necroinflammation, thereby driving liver fibrosis progression [9, 12]. We therefore examined the association between the homozygous genotypes at 3 IFN-λ SNPs, rs12979860, rs8099917, and rs8103142, and the risk for developing significant liver fibrosis (defined as an aspartate transaminase level to platelet count ratio index [APRI] of ≥1.5) in the Canadian Co-infection Cohort (CCC) study.

METHODS

Source Population
The CCC study (n = 1423), established in 2003, is an open prospective cohort of HIV-HCV coinfected individuals recruited from 19 centers across Canada and represents approximately 23% of the coinfected population under care [13]. At visits every 6 months, sociodemographic, medical, and behavioral information is collected using validated questionnaires, along with plasma specimens, serum specimens, and peripheral blood mononuclear cells (PBMCs). For this analysis, we included data collected up until January 2015. To be included in the CCC study, patients must be ≥16 years old, give informed consent, be infected with HIV (confirmed via enzyme-linked immunosorbent assay [ELISA] with Western blot), and have HCV infection or evidence of HCV exposure, defined as follows: HCV antibody–positive ELISA results, using the recombinant immunoblot assay II (RIBA II) or an enzyme immunoassay, or, if results of serological tests are false negative, HCV RNA–positive test results. The study has been approved by research ethics boards at each of the participating institutions.

Study Population and Covariates
Seven hundred and sixty-seven HCV RNA–positive participants free of fibrosis, end-stage liver disease, and chronic hepatitis B at baseline were eligible. HCV RNA levels were tested using qualitative tests (Cobas Amplicor HCV Test, version 2.0; Roche Diagnostics, Hoffmann–La Roche [Laval, Canada]; lower limit of detection, <50 IU mL⁻¹) and were available at most visits. The presence of existing significant fibrosis was determined using an APRI of ≥1.5 at visit 1, while end-stage liver disease was a clinical diagnosis defined as the presence of cirrhosis, ascites, portal hypertension, spontaneous bacterial peritonitis, encephalopathy, esophageal varices, or hepatocellular carcinoma. These diagnoses were verified using specific case report forms and were validated centrally [13]. The presence of hepatitis B virus surface antigen was used to determine chronic hepatitis B virus infection.

Of 767 potentially eligible patients, analyses were restricted to 485 with available genotypes at all 3 SNPs (Figure 1). The APRI, a validated marker of liver fibrosis, was calculated as [([patient’s AST level, in IU/L]/(upper limit of normal AST level, in IU/L)]/ [platelet level, ×10⁹/L] × 100. It consists of routinely available and non-invasive lab markers and was available for almost every visit. Significant fibrosis was defined as developing an APRI of ≥1.5 during follow-up.

Self-reported ethnicity, the strongest expected confounder, was used to categorize patients as white, black, other (Asian or Hispanic Latino), or Aboriginal (First Nation, Metis, or Inuit). Along with ethnicity, we adjusted for other risk factors, including sex, alcohol use (currently drinking or not), baseline age (per decade), dichotomized CD4+ T-cell count (≥350 vs <350 cells/µL), HCV genotype 3 versus other HCV genotypes (ie, HCV genotypes 1, 2, and 4), log-transformed time-updated γ-glutamyl transferase (GGT) level [9], and baseline log-transformed APRI. Variables such as CD4+ T-cell count and HCV genotype were dichotomized at values found clinically relevant in other studies [14, 15].

IFN-λ Genotypes
Never thawed plasma and serum samples were processed and genotyped using a real-time polymerase chain reaction (PCR) assay developed by the Bay Area Genetic Lab, as described previously [5].

Statistical Analysis
Data were evaluated by means of Cox proportional hazards analysis after multiple imputation, using Stata, version 12 [16]. The time axis was calendar time, with the estimated date

Figure 1. Source and study population for examining link between interferon λ genotypes and significant liver fibrosis. Abbreviations: ESLD, end-stage liver disease; HCV, hepatitis C virus; SNP, single-nucleotide polymorphism.
of HCV infection as the origin. Time in the analysis for each patient starts with cohort entry. This method of late entry was used to address the problem of left truncation because half of the cohort had been HCV infected for 17 years at the time of the first visit. HCV infection duration was estimated on the basis of the date of HCV seroconversion, if known, or, depending on the route of HCV acquisition, on the basis of the self-reported year of first injection drug use or first blood product exposure, as a proxy for HCV infection acquisition [17]. Individuals were censored at the last visit if they were lost to follow-up (defined as ≥1.5 years without visit, equivalent to missing 3 consecutive visits) or on the date of death if prior to January 2015. Visits after HCV treatment initiation were censored.

Multiple imputation by chained equations was used to account for missing HCV genotype and other covariates. Data on HCV genotype (for approximately 18% of subjects) and other variables, such as RNA test results (≤15% of subjects) or plasma samples (≤15% of subjects), when missing, were assumed to be missing at random, as the distribution of variables in the analytic population with all 3 SNPs did not vary from that in the source or study population. Before imputation, the frequency of missing data for each of the other covariates in the final model was also <15% among subjects.

A dominant model was used in the association analyses between genotype and significant liver fibrosis. Subjects with 1 or 2 copies of the variant allele were grouped, and the allele(s) was compared to the wild-type genotype. For all 3 SNPs, the homozygous wild-type genotype has been linked to higher HCV clearance and better treatment response. Therefore, for rs12979860, genotype CC was compared to the CT and TT genotypes, whereas for rs8099917 and rs8103142, the TT genotype was compared to the TG and GG genotypes and to the TC and CC genotypes, respectively.

As reported in other studies, we also tested 3 types of interaction: product terms between sex and each genotype [9], age (dichotomized at 40 years) and each genotype [9], and HCV genotype and each genotype [18, 19]. To account for population stratification, we also tested product terms between genotype at each SNP and ethnicity. A sensitivity analysis was performed using age as the time axis, to address uncertainty in the estimated date of HCV acquisition.

Stata, version 12, was used to evaluate Hardy-Weinberg equilibrium, and the software Hapstat [20] was used to test the effect of TCT, the haplotype with the major alleles at all the SNPs (T at rs8103142, C at rs12979860, and T at rs8099917), on liver fibrosis, after adjustment for ethnicity.

RESULTS

Four hundred and eighty-five patients, representing 34% of those enrolled in the CCC study, met final inclusion criteria. One third of the exclusions were due to the presence of existing liver disease at baseline (275 had an APRI of ≥ 1.5, and 58 had prevalent end-stage liver disease). Sociodemographic and clinical factors of those included were similar to those of the cohort as a whole (Table 1). Participants were estimated to have been infected with HCV, predominately genotype 1, for >17 years on average. The majority of the study participants were Canadian-born white males (median age, 44 years), and 83% had a history of injection drug use. Almost half reported drinking some alcohol at baseline. Most were receiving HIV antiretroviral therapy and had well-controlled HIV, with a good CD4+ T-cell recovery (median CD4+ T-cell count at baseline, >350 cells/µL) and an undetectable HIV load. The distribution of the responder IFN-α genotypes was somewhat lower in the study population, compared with that among CCC study subjects as a whole. Alleles at each SNP were in Hardy-Weinberg equilibrium (P > .05).

One hundred twenty-five participants developed fibrosis over 1595 person-years of risk (7.84 cases per 100 person-years; 95% confidence interval [CI], 6.58–9.34). Those who developed significant liver fibrosis were more likely to be female, to be white, and to be injection drug users, compared with subjects who never developed fibrosis (Table 2). They also were more likely to drink alcohol and to have poorer HIV control, as evidenced by the higher proportion with interruptions in antiretroviral treatment and lower CD4+ T-cell counts at baseline. Individuals who developed fibrosis were also more likely to carry rs8099917 TT (ie, the responder genotype), but not rs12979860 CC or rs8103142 TT. At baseline, participants with fibrosis already

### Table 1. Baseline Characteristics of the Canadian Co-Infection Cohort (CCC) and Study Population

| Characteristic                        | Study Population (n = 485) | CCC (n = 1423) |
|---------------------------------------|---------------------------|---------------|
| Follow-up time, y                     | 5 (3–6)                   | 3 (1–6)       |
| Age at baseline, y                    | 44 (38–49)                | 45 (39–50)    |
| Male sex                              | 335 (69)                  | 1026 (72)     |
| White                                 | 369 (76)                  | 1054 (74)     |
| Born in Canada                        | 420 (91)                  | 1114 (90)     |
| History of injection drug use         | 403 (83)                  | 1143 (81)     |
| Current alcohol drinker               | 234 (48)                  | 744 (52)      |
| APRI*                                 | 0.52 (0.37–0.78)          | 0.63 (0.39–1.24) |
| Undetectable HIV load                 | 280 (59)                  | 876 (63)      |
| Receiving HIV-associated ART          | 382 (79)                  | 1178 (83)     |
| CD4+ T-cell count, cells/µL           | 381 (260–550)             | 398 (250–575) |
| HCV infection duration, y             | 17 (10–25)                | 18 (10–26)    |
| HCV genotype 1 infection              | 315 (77)                  | 852 (74)      |
| IFN-α genotype                        |                           |               |
| rs12979860CC                          | 202 (42)                  | 437 (48)      |
| rs8099917TT                           | 297 (61)                  | 599 (65)      |
| rs8103142TT                           | 214 (48)                  | 451 (50)      |

Data are no. (%) of subjects or median value (interquartile range).

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN-α, interferon-α.

* The aspartate aminotransferase (AST) level to platelet count ratio index (APRI) was calculated as ([patient’s AST level, in IU/L]/upper limit of normal AST level, in IU/L]/[platelet level, ×10^9/L] × 100.

b Limit of detection, ≤50 copies/mL.
had higher median APRI scores, compared with those who never reached an APRI of >1.5.

In univariate analysis, rs8099917 had the strongest association. Since both rs12979860 and rs8103142 are very close together and tightly linked (r² = 0.81 among whites in our cohort [5] and r² ≥ 0.85 in other studies [6, 21]), their effect estimates were almost identical and thus were analyzed separately. None of the other product terms between the SNPs and age, sex, HCV genotype, or ethnicity indicated effect measure modification (P > .05).

As with the individual SNPs, the results from the haplotype analysis indicated that participants with a haplotype with the major alleles from all 3 SNPs (TCT) had a higher risk of fibrosis than those lacking the haplotype, regardless of the mode of inheritance. The log likelihood values are very similar (Table 3), but based on the dominant model, those with 1 or 2 copies of TCT had a 14% higher risk of fibrosis than those with no copies (hazard ratio, 1.14; 95% CI, 0.73–1.77).

Other than IFN-λ genotype, log-transformed GGT level, which is a marker of oxidative stress, and baseline APRI had the strongest effects, with each log increase associated with a tripling of risk. Being female or of younger age was associated with a higher risk of fibrosis, after accounting for HCV duration. Being infected with HCV genotype 3 or currently drinking alcohol also raised risk of fibrosis by >40%, compared with infection with HCV genotypes 1, 2, or 4 or no current drinking of alcohol, respectively. Those with well-controlled HIV, evidenced by CD4⁺ T-cell counts of ≥350 cells/µL, were 30% less likely to develop significant fibrosis than those with CD4⁺ T-cell counts of <350 cells/µL (Table 4).

**DISCUSSION**

We found that coinfected persons without liver fibrosis at baseline who carry major alleles in any of the IFN-λ SNPs were at increased risk of developing significant liver fibrosis even after accounting for major known risk factors of fibrosis progression. This relationship between IFN-λ SNPs that have been associated with proinflammatory responses and risk of liver fibrosis was present independently of the baseline APRI score, suggesting the SNPs may be valuable markers for identifying patients who could benefit from curative HCV therapy.

SNPs of interest included those at rs12979860 and rs8099917, which are located in the noncoding region of IFNL3, and 1 at rs8103142, which leads to a nonsynonymous amino acid change. While genotypes at all SNPs were linked with higher fibrosis, rs8099917 had the strongest association, with the TT genotype almost doubling the risk of fibrosis. Previous studies examining the association between the SNPs and fibrosis progression, mainly in monoinfected populations, have yielded mixed results, possibly due to low power [11] or selection bias, where study recruitment depended on having no response to previous HCV treatment or having advanced liver disease, thus possibly enriching the population with individuals who had nonresponder genotypes [8]. In contrast, ours is the largest longitudinal study of coinfected individuals in which recruitment was independent of eligibility for HCV treatment.

Several cross-sectional and cohort studies have suggested effect sizes similar to those we observed. In these other studies, the strongest relationships (odds ratio, 1.93 with rs8099917T) were
those reported in coinfected patients [10], although odds ratios for rs8099917 from monoinfected populations were also >1.5 [19]. A large study involving 3129 patients without HIV infection (and 1500 fibrotic outcomes) reported that rs12979860CC and rs8099917TT were associated with a >60% increase in risk of fibrosis [9]. In this study, IFN-λ genotypes were predictive of fibrosis independent of disease etiology, as they were equally predictive in individuals with HCV infection, as well as in those with hepatitis B virus infection or nonalcoholic fatty liver disease [9]. This suggests that even with clearance of HCV after therapy, individuals with the IFN-λ responder genotypes may remain at higher risk for fibrosis, especially in the presence of other hepatotoxic behaviors or insults, many of which exist in drug-using or coinfect ed populations. Thus, these individuals may warrant closer follow-up after treatment for liver disease outcomes.

The mechanism of IFN-λ SNPs remains an active research area. IFN-λ3 is a type III interferon effective against viruses such as HCV and HIV [22, 23]. Additionally, IFN-λ3 turns on IFN-stimulated genes needed for viral control [12]. Some variants that have been proposed as the causal mechanism include rs368234815 (IFNL4) [21], which affects IFN-λ3 responsiveness, or rs8103142, which leads to amino acid substitutions in IFN-λ3 and could affect interactions with other unknown factors involving viral control [12, 24]. In populations where there is strong correlation (ie, linkage disequilibrium) between these causal SNPs and markers such as rs12979860 and rs8099917, there is a higher likelihood of HCV clearance, indicating a strong and responsive immune mechanism.

It is difficult to untangle the effects of these SNPs on protein function or fibrosis development without a functional study, although our findings are consistent with several possible mechanisms. The genotypes linked with higher fibrosis risk in our study could be serving as markers for inflammatory pathways, because fibrosis progression is caused by heightened inflammation rather than by HCV replication. For example, several studies have shown that the responder IFNL3 polymorphisms are predictors of elevated histological inflammatory activity [9, 18]. In addition, responder alleles at rs12979860 turn on genes involved in natural killer cell activation, resulting in apoptosis of infected hepatocytes and a proinflammatory environment [25]. Although these events are potent for clearing HCV, in the presence of viral persistence, as seen in the patients included in our analysis, they can also cause and exacerbate liver injury.

Results from a few in vitro studies [24, 26] indicate that the function of IFN-λ3 is unaffected by the K70R (lysine-arginine) amino acid substitution tagged by rs8103142. However, one of the studies only examined this in a single experimental model within a short time frame (24 hours), and thus the authors did not rule out a major role for the Lys70Arg variant in treatment or immune response [24]. Nevertheless, it is also possible that the alleles from rs8103142 or rs12979860 are linked with other causal variant(s) in the IFNL3 region, such as rs368234815, which encodes IFN-λ4 [21]. The antiviral activity of IFN-λ3 and IFN-λ4 is linked with higher levels of interferon-stimulated gene expression [21], and although this has been linked with improved HCV clearance, it is not known whether this vigorous immune response contributes to fibrosis progression. It is also possible that, as the SNP at rs8099917 is less tightly bound to both IFN-λ3 and IFN-λ4 (r² = 0.39 among white individuals in our cohort [5] and approximately 0.40 in other studies [21]), it could be tagging the effect of other causal variants from fibrogenic pathways.

Our study population was selected from one of the largest prospective cohorts of HIV–HCV–coinfected individuals in the world and one that was representative of the Canadian coinfected population, including marginalized groups such as people who inject drugs and Aboriginal people. Because of regular longitudinal follow-up, we were able to measure risk factors of fibrosis progression that could potentially be combined into a
progression index and investigated in future studies. By including individuals who acquired HCV remotely, we were also able to avoid the referral bias of previous retrospective studies. Those studies overestimated the severe outcomes of HCV infection (cirrhosis, hepatocellular carcinoma, and death) and did not allow for the examination of those who spontaneously recover from their infection or have milder forms of the disease [27]. Our study thus has characteristics of a prospective cohort but allows long-term follow-up that rarely can be achieved in prospective studies. Our study population was very similar to that in the CCC study overall, so our results should be reasonably generalizable to coinfected individuals receiving care in Canada. However, although the CCC study attempts to recruit from diverse populations, including patients with various risk factors and who are marginalized, persons not accessing care may differ from those included in our analyses.

A potential limitation in our study is the possibility of selection bias induced through the exclusion of individuals with spontaneous HCV clearance and prevalent liver disease, who are more likely to have the genotypes of interest. However, results from an analysis in data sets with limited or no exclusions were very similar to those reported in Table 4, indicating that any selection bias was likely negligible (results not shown).

Another important issue is the possibility of residual confounding by ethnicity because of the diverse ancestries of our participants. We attempted to address this by adjusting for self-reported ethnicity. Furthermore, after restricting analyses to white individuals only or stratifying for ethnicity in sensitivity analysis, the effect estimates obtained were similar to those in Table 4 although less precise (not shown), suggesting that such confounding is unlikely to have been great.

Another possible limitation in our study is the use of the APRI to measure the outcome. Liver biopsy, the gold standard for measuring liver fibrosis, is invasive, risky, and subject to measurement error, thus making it impractical for longitudinal research purposes. Without biopsy samples, we were also unable to assess the degree of hepatic necroinflammation. Fibroscan data were not available in sufficient numbers of patients to permit longitudinal analyses. However, an APRI cutoff at 1.5 (corresponding to F2 in the METAVIR scoring system) has been validated in our study population for detecting significant liver fibrosis, with a sensitivity of 52%, a specificity and positive predictive value of >99%, and a mean area under the curve (+SD) of 0.85 ± 0.06 [28]. In addition, APRI cutoffs of 1.5 and 2 have also been shown to be associated with cirrhosis, other adverse liver and clinical outcomes, and death in our cohort [29], as well as in other studies [30, 31]. Using an APRI of ≥1.5 also allowed us to potentially capture the etiologically relevant transition to fibrosis stage F2, as IFN-λ genotypes were reportedly more important in earlier fibrosis transitions (F0–F1 and F1–F2), rather than later ones (F2–F3 and F3–F4) [9]. Alternative noninvasive markers such as FIB-4 (>3.25) correspond to more-advanced fibrosis stage (F3 and higher), missing the F1–F2 transition [32]. Applying FIB-4 to these analyses therefore resulted in a lower sample size and less precise estimates, with the strongest association at rs8103142 (adjusted hazard ratio, 1.14; 95% CI, 0.71–1.83). Finally, measurement error in APRI is likely independent of IFN-λ genotype (the main exposure group) and would be nondifferential and thus potentially underestimate a true causal effect.

There was uncertainty in the estimate of the date of HCV acquisition, which was approximate in most instances and used as the origin. Because this date preceded cohort entry by many years, it also led to left truncation, which we addressed by using delayed entry in our analysis. Moreover, results from the sensitivity analyses using age as a time axis were very similar to those in Table 4 (data not shown). Finally, while other risk factors in our results, such as alcohol use and HCV genotype 3 infection, are consistent with other studies [14, 15, 33, 34], we lacked the power to detect the interaction of IFN-λ genotypes with sex, age, HCV genotypes, or ethnicity [9, 19].

In conclusion, our results suggest that the homozygous genotypes at the IFN-λ SNPs rs8099917, rs12979860, and rs8103142 individually increased the risk of significant liver fibrosis in HIV-HCV–coinfected Canadians. The association of rs8099917-TT was strongest, with almost a doubling of risk. Our findings are consistent with a heightened inflammatory profile and could help identify higher-risk individuals who would benefit the most from expensive HCV direct-acting antiviral agents before liver disease advances to the point of no return.

STUDY GROUP MEMBERS

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N. M. and M. B. K. designed the study. N. M. drafted the manuscript and conducted all the analyses, with help from R. W. P. and M. B. K. All authors commented on the manuscript.

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