

Review Article

Geographical and genetic diversity of the human hepatitis B virus

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Hepatitis B virus (HBV) is one of the most widely distributed viruses that infect humankind. Distinct clinical and virological characteristics of the HBV-infection have been reported in different geographical parts of the world and are increasingly associated with genetic diversity of the infecting virus. HBV is classified into genotypes and subgenotypes that are associated with ethnicity and geography. The genetic diversity of HBV in its various aspects has been the subject of extensive investigations during the last few decades. Since molecular epidemiology research tools have become widely available,

the number of new publications in this field has grown exponentially. This review summarises the recent publications on the geographical distribution of genetic variants of HBV, and proposes updated criteria for the identification of new genotypes and subgenotypes of the virus.

Key words: genotypes, hepatitis B virus, molecular epidemiology, recombination

INTRODUCTION

FOUR DECADES AGO, in 1965, the “Australian antigen” (now referred to as the hepatitis B surface antigen, HBsAg) was detected in hemophilia patients¹ and was soon specifically associated with hepatitis B virus (HBV).^{2,3} Three decades ago, the HBV strains were divided into nine major serotypes based on antigenic determinants of HBsAg.⁴ Two decades ago, the classification of the HBV by genome nucleotide sequence divergence was proposed.⁵ A decade ago, a “unique phylogenetic cluster within genotype A strains was described, triggering consecutive investigations on HBV subgenotypes.”⁶

Outlined are the most important key-events in a chain of findings that accumulated in the current image of the HBV diversity. The chain was tortuous before powerful tools such as PCR and nucleotide sequencing became available to researchers. These tools enabled the annual

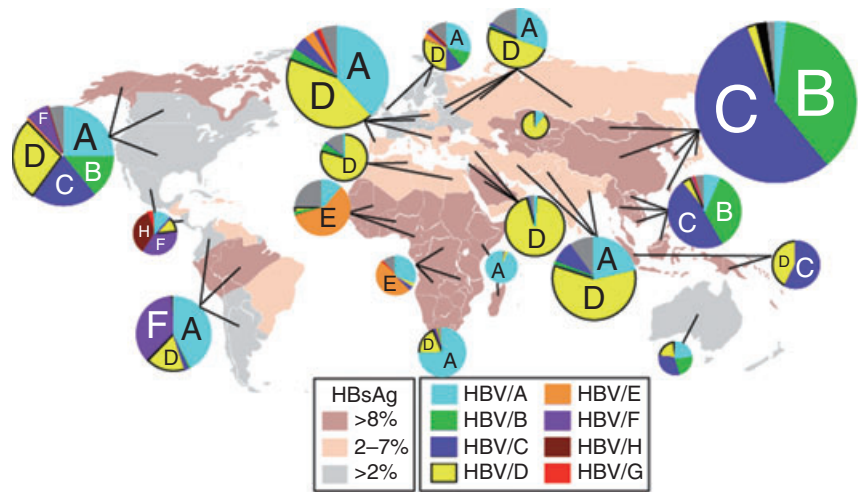
number of publications in this field to grow exponentially. The current review will discuss the most recently published observations on HBV diversity, particularly their geographical distribution, and taxonomical aspects.

CURRENTLY KNOWN HBV GENOTYPES

A TOTAL OF 18 complete genome sequences were available for comparison when the first four genotypes of HBV (designated A to D, consecutively) were originally proposed and divergence exceeding 8% of the complete genome was indicated as a criterion for genotype identification.⁵ Almost at the same time, genotyping based on the phylogenetic clustering was proposed.⁷ Consecutively, by sequencing the HBsAg coding region, four new strains were designated as novel genotypes E and F based on both, percent evaluation of nucleotide divergence and phylogenetic analysis. This added new criteria for genotyping; 4% of nucleotide divergence in HBsAg coding sequence.⁸ Shortly after, the genotype F was confirmed by an analysis of the full genome sequence.⁹ Relatively recent reports identified the last two of the 8 currently known genotypes, genotype G¹⁰ and H.¹¹

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Figure 1 Hepatitis B virus (HBV) infection endemicity is based on the 2005 estimation of hepatitis B surface antigen (HBsAg) seroprevalence (Centers for Disease Control and Prevention Travelers' Health: Yellow Book Chapter 4 – Prevention of Specific Infectious Diseases: Hepatitis, Viral, Type B URL: <http://wwwn.cdc.gov/travel/yellowbook/ch4/hep-b.aspx>). Percentile distribution of genotypes is indicated for each geographic region.



DISTRIBUTION OF GENOTYPES IN THE WORLD

EPIDEMIOLOGICAL GEOGRAPHICAL DISTRIBUTION of HBV genotypes is being continuously investigated in different parts of the world. For this review we summarised epidemiological studies published within the last decade. A total of 256 papers were analysed. The results of the geographical distribution of

genotypes are graphically summarised in Figure 1A. The detailed summary presented in Table 1 contains the number of examined HBV carriers in each particular subregion, and the corresponding references.

The total number of HBV-infected individuals genotyped during the last 10 years consist of approximately 45 000, with more than half of that number in Eastern Asia. From the data accumulated, it can be seen that a single genotype can only be predominately found in

Table 1 Prevalence of hepatitis B virus genotypes in different geographical regions

Geographical subregion	n	A	B	C	D	E	F	H	G	Mixed	UT	References
Eastern Africa	43	93.0			2.3						4.7	12–14
South Africa	404	74.3	0.7	1.5	19.3	1.2					3.0	15–17
Central Africa	126	31.0		3.2	3.2	49.2			1.6	11.9		18–20
Western Africa	759	11.3	0.3		1.6	59.2				2.9	24.8	21–29
Northern Africa	331	0.3	5.7	0.9	79.2					9.4	4.5	30–34
Western Asia	1652	0.9	0.2	0.5	94.8		0.1				3.5	35–58
Central Asia	118	11.0		0.8	88.1							59–61
Southern Asia	3023	21.5	0.9	8.9	58.7					3.9	6.1	25,62–79
East Europe	1674	30.5	0.9	0.7	50.4					6.0	11.5	25,80–86
European Union	4968	38.5	3.3	4.3	42.6	3.4	1.4	0.2	0.7	2.0	3.7	10,20,25,81,87–116
North Europe	442	28.3	10.9	10.6	30.8	5.0	1.4	0.2	0.2	2.0	10.6	117–122
North America	3412	25.1	14.3	20.8	27.7	0.2	7.3	0.1	0.9		3.6	10,25,108,123–131
Central America	225	11.6		0.4	11.6		36.0	35.1	3.6	1.3	0.4	132–135
South America	1393	42.6	0.5	1.9	17.4	0.1	35.9		0.1	0.6	0.9	25,136–157
Atlantic Island	84	54.8		1.2	23.8		2.4			17.9		110
Southeastern Asia	2024	6.7	35.2	47.3	4.1	0.7	0.4		0.9	3.4	1.2	20,25,108,158–170
Eastern Asia	23577	2.0	36.9	55.0	2.2					1.9	1.9	25,108,171–255
Pacific Islands	274			57.7	42.3							225,239,256,257
Australia	132	22.7	22.7	31.8	21.2				0.8		0.8	258–260
TOTAL	44661	13.1	22.9	34.5	19.9	1.6	2.1	0.2	0.2	2.1	3.3	

UT, untypeable

Eastern Africa and Western Asia (A and D, respectively) where the prevalence of other genotypes was less than 5%. On the other hand, in countries with high levels of immigration, a variety of genotypes are being reported; all of the known genotypes can be found in the Europe and North America. In Australia, genotypes A, B, C and D were reported in equal prevalence. Two genotypes, A and D are prevalent in European Union (except for the Mediterranean where D predominates), and in Central/Southern Asia. Genotypes B and C are the major variants in South and South East Asia and the Pacific region, while genotypes A and F are the most common in South America or E and A in Central Africa. Genotype E is restricted to Central and West Africa however, its prevalence tends to increase in Europe. Genotype F is subdivided into 4 subgenotypes, and is prevalent in Central and South America and Alaska. In recent reports the subgenotypes of genotype F were further subdivided into clades (Table 2).

A recent study from Peru described a full genome analysis for three strains from Peru that belonged to subtype F1 and suggested they should be considered as clade 1c within subgenotype F1.²⁸¹ Genotype G was found in Europe and the United States. A few cases of genotype G infection have been reported from Asia,^{227,283} and more recently from Brazil.²⁸⁴ Despite the geographical dispersion of the reported G strains, they show a very low genetic diversity. Genotype H is frequent in and restricted to Central America where it was also reported in co-infection with genotype G.¹³³ The pattern of genotype distribution changes according to the pattern of global migration.

EVOLUTIONARY HISTORY OF THE GENOTYPES

THE FIRST ATTEMPT to date the evolutionary history of HBV was carried out by the phylogenetic analysis based on synonymous substitutions in the polymerase coding gene of hepadnavirus family strains isolated from the human, chimpanzee, woodchuck, ground squirrel and duck.⁷ The substitution rate estimated in the study was 4.57×10^{-5} substitutions/site/year. This study concluded that the duck strain was the most divergent and shared the most recent common ancestor with other strains approximately 30 000 years ago, whereas different human HBV genotypes emerged about 3000 years ago.⁷ However, the overlapping composition of Open Reading Frames (ORFs) in the HBV genome complicates an estimation of the synonymous substitutions, as the same mutation considered synonymous in

one of the ORF may cause an aminoacid change in overlapping ORF.²⁸⁵ The mutation rate of HBV estimated in the serial specimens collected at distant periods of time from genotype B infected carriers, was 7.9×10^{-5} substitutions/site/year.²⁷¹ Another study carried on genotype D strains representing localised epidemic in Western Japan, have set the mutation rate to 5.4×10^{-5} .²⁷⁷ A study aiming to estimate the substitution rate using two independent data sets of non-overlapping ORF coding core protein, concluded that a reliable molecular clock does not exist.²⁸⁶ Phylogenetic topology of the genotypes heavily depends on the genomic region and substitution model used in analysis, thus hinder any attempt to reconstruct the past spread of this virus.²⁸⁶ In addition to the complex overlapping structure of the genome, a recombination of HBV severely hampers an assessment of its evolution.²⁸⁷ New methodological approach is required to explore rules of the HBV evolution.

HBV RECOMBINATION

ONE OF THE most comprehensive analyses of occurrence and composition of HBV intergenotype recombinants indicated the existence of 24 phylogenetically independent recombinant forms of HBV involving all human genotypes as well as both chimpanzee and gibbon variants.²⁸⁸ Further reports are constantly extending this number.^{18,118,283,289} It has been shown that 60% of the intergenotype recombinants have the breakpoints within nucleotides 1640–1900.²⁸⁹ It was also concluded that recombination sites often localise to gene boundaries.^{288,289} Further, using a newly developed approach (“TreeOrder Scan”) the authors could demonstrate that analysed in different parts of the HBV genome, genotypes are interchangeably shifting the relative phylogenetic topology. This consists with changes in the overall phylogenetic topology of the HBV genotypes that can be observed in trees reconstructed from different parts of the genome. Genotype G strains in particular demonstrate evidence of recombination with genotype A in the Small S fragment (nucleotides: 250–350) as well as genotype E with genotype D in the core gene (nucleotides: 1950–2500) and genotype H with genotype F within the *Small S* gene (nucleotides: 350–500).²⁸⁸ It was hypothesised that some of the genotypes that are conventionally regarded as “nonrecombinant,” demonstrate evidence of recombination, that is, during evolution in some cases, one or other of the ancestral HBV variants that might have been involved in recombination are virtually replaced by a more viable

Table 2 Hepatitis B virus (HBV) subgenotypes

Genotype	Subgenotype	n	Complete genome Nucleotides diversity (complete genome)			Geography	Ref
			Clustering	Intra-subgenotype mean + SD (max)	Next closest neighbour mean + SD (min)		
HBV/A	A1/Aa	78	yes	2.6 + 0.8 (5.5)	4.4 + 0.4 (3.3) for A4	Africa, Asia, South America	15,261,262
	A2/Ae	94	yes	1.7 + 0.9 (5.5)	4.7 + 0.7 (3.6) for A4	Europe, North America	15,261,262
	A3/Ac	8	yes	3.0 + 0.9 (4.1)	4.7 + 0.4 (3.8) for A1	Western Africa	19,21,22
	A4	3	no	2.9 + 0.9 (3.5)	3.8 + 0.2 (3.4) for A3	Western Africa	21,263
	A5	0	?	?	?	Western Africa	21
HBV/B	B1/Bj	38	yes	2.4 + 0.6 (4.1)	4.6 + 0.5 (3.6) for B2	Japan	264–266
	B2	173	yes	1.7 + 0.8 (4.0)	4.4 + 0.5 (2.9) for B4	China, Taiwan	190,200,264–268
	B3	5	yes	1.6 + 0.6 (2.7)	3.6 + 0.5 (2.9) for B5	Indonesia	269
	B4	21	yes	2.7 + 0.6 (4.4)	5.0 + 0.5 (4.3) for B3	Vietnam, Cambodia	269
	B5	7	yes	2.8 + 1.5 (4.5)	5.2 + 0.6 (4.0) for B2	the Philippines	166,167
	B6	27	yes	2.7 + 0.7 (4.2)	5.7 + 0.6 (4.6) for B3	Native populations in Arctic	270,271
	B7	2	no			Indonesia	161
HBV/C	C1/Cs	97	yes	2.4 + 0.7 (5.1)	4.4 + 0.5 (3.1) for C2	South and South East Asia	272–274
	C2/Ce	295	yes	2.5 + 0.6 (4.7)	4.9 + 0.5 (3.8) for C3	Eastern Asia (Korea, Japan) and North China	
	C3	3	yes	4.2 + 1.2 (5.2)	5.8 + 0.6 (4.6) for C1	Pacific	269
	C4	2	yes	0.9	6.6 + 0.6 (6.0) for C3	Australia	256
	C5	8	yes	2.0 + 1.0 (3.4)	6.2 + 0.5 (5.0) for C1	Philippines, Vietnam	167
HBV/D	D1	88	yes	2.3 + 0.8 (5.2)	3.1 + 0.6 (1.7) for D2	North Africa, Europe, Central Asia	84,269,275
	D2	53	yes	3.0 + 0.8 (5.8)	4.2 + 0.6 (2.6) for D3	North Europe, Russia, Japan (Ehime)	269,276–278
	D3	66	yes	2.9 + 1.1 (5.9)	4.1 + 0.7 (2.3) for D1	South Africa, Europe	
	D4	7	yes	2.6 + 1.2 (4.9)	4.6 + 0.6 (3.5) for D1	Australia	256
	D5	2	yes	2.4	5.2 + 0.5 (4.9) for D4	Eastern India	73
HBV/F	F1a	4		1.1 + 0.2 (1.4)	2.0 + 0.2 (1.6) for 1b	Central America: Costa Rica	279,280
	F1b	7		0.4 + 0.1 (0.6)	1.9 + 0.3 (1.5) for 1d	Venezuela, Argentina, Alaska	154,279,281,282
	F1d	2		2.2	2.8 + 0.3 (2.4) for 1a	Japan	279,281
	F2a	9		1.1 + 0.3 (1.4)	3.2 + 0.2 (2.8) for 2b	Brasil, Venezuela, Nicaragua	24,154
	F2b			0.5 + 0.1 (0.6)	4.1 + 0.9 (2.8) for F4		
	F3	23	yes	1.1 + 0.9 (4.2)	4.5 + 0.3 (3.9) for F2	Venezuela	
	F4	6		1.9 + 0.9 (3.7)	4.6 + 0.6 (3.8) for F3	Argentina, Bolivia	142

product of the recombination. Discovery of “pure” genotypes E, G or H strains would confirm this hypothesis. Most of the studies that have found a high prevalence of both D and E were reported in Europe, in particular France.^{92–95,103} The only country less affected by recent migration is Cameroon, where these two variants might have been endemic for a longer period of time. However, sequencing of a number of Cameroonian HBV/E strains to date did not reveal any evidence of the presence of a “pure” genotype E that is not “sharing” its core gene sequence with genotype D.^{21,22} Genotypes G and H have the highest prevalence in Mexico,^{133,134} a country where genotypes A and F are also prevalent.^{132,290} Hence further molecular epidemiological studies in Cameroon and Mexico may reveal traces of “pure” non-recombinant ancestors of currently known genotypes.

GENOTYPES COINFECTION

AS MORE THAN one genotype is predominant in most of the geographic regions, coinfection between the predominating genotypes is not a rare finding; especially for B and C,^{169,176,179,202,223,251,291} or A and D.^{19,21,27,63,69,70,77,79,105,110,138,139} Co-infections with different genotypes of HBV are being reported with various frequencies. The frequency, however, seems to have a stronger association with the genotyping method rather than a geographic region or genotype endemic in a studied population. Most of the reported cases of co-infection with different genotypes were detected by using multiplex PCR or hybridisation assays and are rarely confirmed by conventional cloning and sequencing.^{20,81,95,206} However, genotyping based on PCR with specific primers, probes, and/or restriction enzymes may produce misleading non-specific results due to single nucleotide polymorphisms. This is particularly important in case the PCR-based genotyping assays are applied when studying populations with only a few representing HBV sequences in the database, which means that the local variability of HBV strains was not considered when the assay was designed. In some reports, coinfections detected between genotypes not endemic in the studied population. A cross-sectional international population study using PCR-RFLP genotyping, reported 10/47 cases of genotype C in African cohorts and 6 of the 10 cases were found in coinfection (mainly with genotype G.)²⁰ The same study detected genotypes E to be more frequent in Asian cohorts compared to European and African ones.²⁰ However these findings are discrepant with previous reports on the geographical distribution

of the genotypes therefore the result obtained by PCR-based genotyping assay requires confirmation by cloning and sequencing.

SUBGENOTYPES

GENETIC VARIABILITY WITHIN the genotypes is being extensively investigated since the concept of subgenotyping has evolved from studies on genotype A^{15,261} and B.²⁶⁶ All genotypes except for E, G and H are currently subdivided into subgenotypes (Table 2). Analysis of accumulated sequence data of HBV indicated that nucleotide sequence divergence exceeding 4% but less than 7.5% in the entire genome sequence should be used as criterion for identifying subgenotypes, whereas divisions within the subgenotypes showing less than 4% divergence should be referred to as “clades.”²⁶² In this view, the recently proposed subgenotype A4²¹ with a mean and minimal nucleotide divergence from subgenotype A3; 3.8% and 3.4%, respectively, is a clade rather than a subgenotype (Table 2). This can be further supported by a phylogenetic tree constructed on the complete genome of the strains, showing the “A4” strains to group along with the A3 strains (Fig. 2). Similar geographic distribution of the strains (West Africa) concurs that “A4” and A3 strains represent the same subgenotype. The small genetic distance and similar endemicity of the recently proposed subgenotypes B3, B5 and B7 can also suggest that these can be considered as clades representing the same subgenotype of genotype B (Table 2).

EVOLVING OF GENOTYPING CRITERIA

AN EXTENSIVE ANALYSIS of accumulated HBV genome sequence data indicated that the nucleotide diversity of genotype H strains is less than 8% from its closest neighbour; genotype F.²⁷⁹ It was further proposed to use 7.5% of nucleotide divergence in the complete genome as a cut off for designation of new genotypes.²⁶² A new genotype “I” was recently reported to be circulating in Vietnam.²⁹⁴ However, the conclusions of the paper on the new genotype and on the complex intergenotypic recombination did not correspond with existing genotyping criteria.²⁹⁵ First of all, the complete genome genetic diversity of the strain was lower than 7.5% from the closest neighbour; genotype C (7.0%). Second, the genetic recombination with other genotypes was evident.^{288,295,296} And finally, the epidemiological significance of the aberrant variant in terms of a new genotype was questionable as only three strains

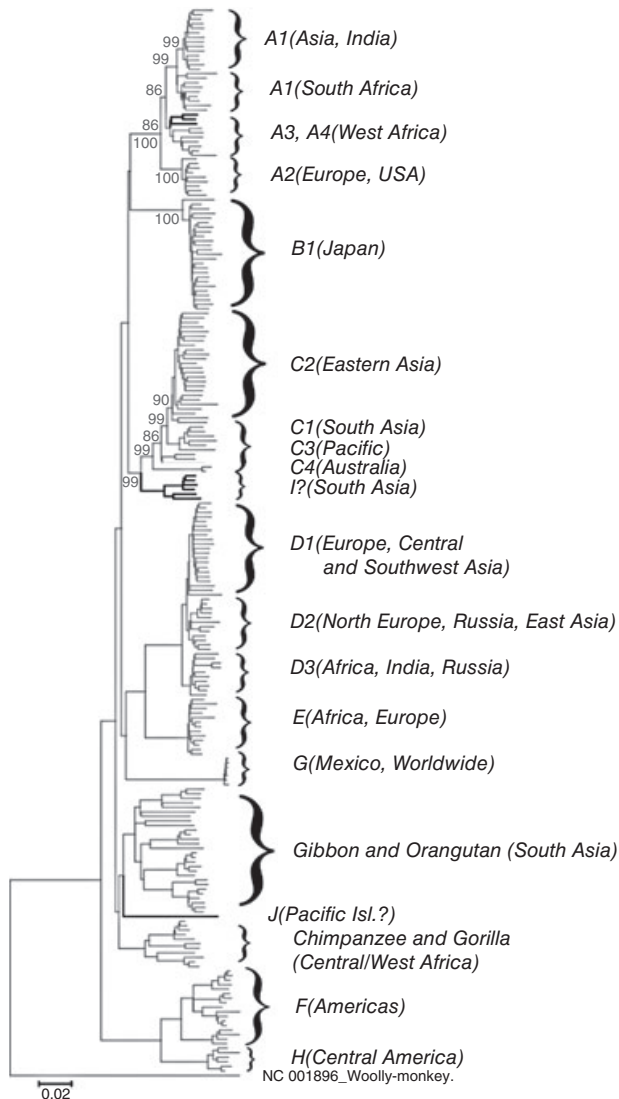


Figure 2 Phylogenetic tree constructed on selected complete genome strain references, which had no evidence of recombination. The neighbour joining tree was constructed using online aligning and tree drawing tools.^{292,293}

have been reported during the 8 years since the first report describing this variant.²⁹⁶ More recent study carried in Laos have revealed more strains that are genetically similar to the three Vietnamese isolates, providing evidence for the epidemiological value of the specific designation of the variant.²⁹⁷ However, further studies are required to justify the classification of the variant into a separate genotype (HBV-I) or to consider it as a subgenotype of the existing genotype (HBV-C) (Fig. 2.) Another recent study from Japan, based on a

strain isolated from a hepatocellular carcinoma patient who had a history of travelling to Borneo, revealed a novel genetic variant of HBV phylogenetically positioned between clusters of human and primate isolates.²⁹⁸ The tentative genotype J strain show no evidence of recombination with any of known genotypes, and it is phylogenetically close to strains previously isolated from Gibbons and Orangutan (Fig. 2.) Epidemiological, virologic and clinical features of both provisional genotypes I and J require further studies to justify their classification.

Alternative approaches for the genotyping of HBV were recently proposed, suggesting that known variants of HBV can be grouped into 4 groups²⁹⁹ or 3 groups,³⁰⁰ however, the relevance of these classifications still needs to be substantiated from epidemiological and clinical points of view.

GENOTYPING CRITERIA

INTENSIVE INVESTIGATIONS HAVE indicated an uneven geographical distribution and epidemiology of distinct HBV genotypes and subgenotypes, however, many questions remain unanswered in terms of their virologic and clinical features. Further investigations in this field require standardised criteria for genotyping and subgenotyping, and these criteria need to be updated regularly in the context of new findings. Currently we propose the following check list of minimal requirements for defining genotypes and subgenotypes:

- 1 A complete genome sequence analysis is required to identify a new genotype or subgenotype.
- 2 Nucleotide divergence in a complete genome should exceed 7.5% to distinguish a genotype or 4% to distinguish a subgenotype. Variability below 4% confirmed by specific phylogenetic clustering can be used as a criterion to identify clades within subgenotypes.
- 3 Genotypes and subgenotypes should be identified by robust independent clustering on molecular evolutionary analysis based on complete HBV genomes.
- 4 Evidence of recombination with other known or unknown genotypes should be used as a criterion for identifying a subgenotype or clade of genotype involved in recombination rather than a new independent genotype.
- 5 Identification of a new genotype should be substantiated by its epidemiological, virological or clinical characteristics.

In conclusion, HBV demonstrates significant genetic and geographical divergence. Further studies are required to investigate genetic characteristics of the virus

in less studied developing countries, especially those with a high endemicity. Updated unified criteria are required to resolve future issues in genotype assignment.

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