

Supplementary Material

Supplementary Figure S1

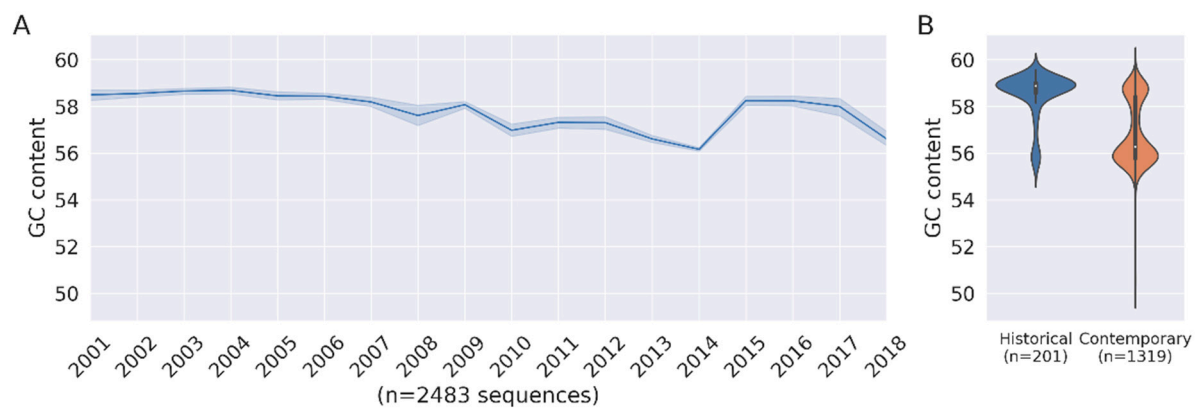


Figure S1: GC content of HCV genomes over time: **A.** Line plot showing the GC content of HCV genomes from samples collected during 2001 to 2018, **B.** Violin plots with GC content of historical and contemporary sequences ($p < 0.0001$).

Supplementary Figure S2

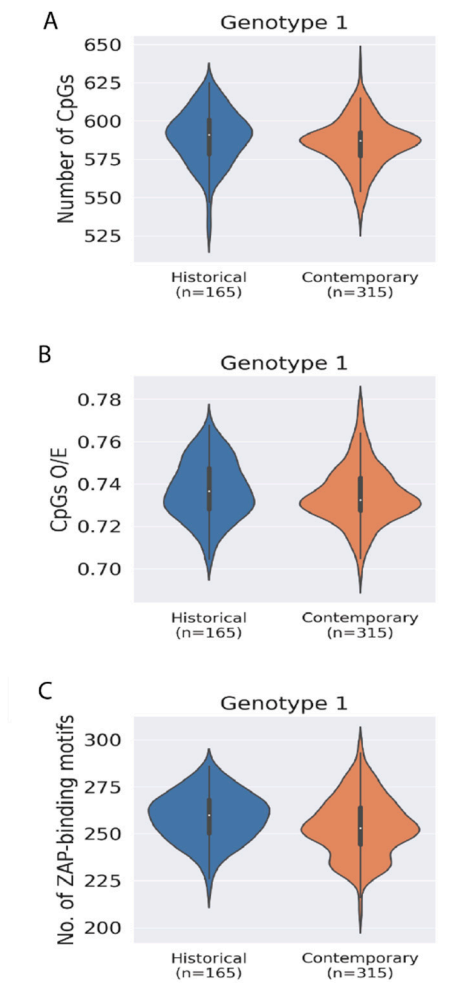


Figure S2: Analysis of HCV genotype 1: Violin plots comparing **A.** CpG numbers ($p = 0.004$), **B.** CpG O/E ($p = 0.04$), **C.** Number of ZAP binding motifs ($p = 0.0002$) between historical sequences to contemporary from HCV genotype 1.

Supplementary Figure S3

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1  GCCAGCCCCC TGATGGGGGC GACACTCCAC CATGAATCAC TCCCCTGTGA GGAAC TACTG
61  TCTTCACGCA GAAAGCGTCT AGCCATGGCG TTAGTATGAG TGTCGTGCAG CCTCCAGGAC
121 CCCCCCTCCC GGGAGAGCCA TAGTGGTCTG CGGAACCGGT GAGTACACCG GAATTGCCAG
181 GACGACCGGG TCCTTTCTTG GATAAACCCG CTCAATGCCT GGAGATTTGG GCGTGCCCCC
241 GCAAGACTGC TAGCCGAGTA GTGTTGGGTC GCGAAAGGCC TTGTGGTACT GCCTGATAGG
301 GTGCTTGCGA GTGCCCCGGG AGGTCTCGTA GACCGTGCAC CATGAGCACG AATCCTAAAC
361 CTCAAAGAAA AACCAAACGT AACACCAACC GTCGCCCCACA GGACGTC AAG TTCCCGGGTG
421 GCGGTTCAGAT CGTTGGTGGA GTTTA CTTGT TGCCGCGCAG GGGCCCTAGA TTGGGTGTGC
481 GCGCGACGAG GAAGACTTCC GAGCGGTGCG AACCTCGAGG TAGACGTCAG CCTATCCCA
541 AGGCACGTCG GCCCGAGGGC AGGACCTGGG CTCAGCCCGG GTACCCCTTG CCCCTCTATG
601 GCAATGAGGG TTGCGGGTGG GCGGGATGGC TCCTGTCTCC CCGTGGCTCT CGGCCTAGCT
661 GGGGCCCCAC AGACCCCCGG CGTAGGTCG GCAATTTGGG TAAGGTCATC GATACCCTTA
721 CGTGCGGCTT CGCCGACCTC ATGGGGTACA TACCGCTCGT CGGCGCCCT CTTGGAGGCG
781 CTGCAGGGC CCTGGCGCAT GGCGTCCGGG TTCTGGAAGA CGGCGTGAAC TATGCAACAG
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901 TGCCCGCTTC AGCCTACCAA GTGCGCAATT CCTCGGGGCT TTACCATGTC ACCAATGATT
961 GCCCTAACTC GAGTATTGTG TACGAGGCGG CCGATGCCAT CCTGCACACT CCGGGGTGTG
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1861 ATTGCTTAC TCCAGCCCC GTGGTGGTGG GAACGACCGA CAGGTCGGGC GCGCCTACCT
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 9601 **GCATG**ACTGC AGAGAGTGCT GATACTGGCC TCTCTGCAGA TCATGT

Figure S3. Analysis of conservation of ZAP-binding motifs in the HCV reference sequence (NC 004102): Sequences marked in red are ZAP-binding motifs, and the bold sequences are the ZAP-binding motifs that are conserved across at least 75% of the 2616 sequences analysed.