**Supplementary Legends:**

**Supplementary Table 1**. Metadata information of viral isolates including date of collection, province, genotype used in this study.

**Supplementary Table 2**. Annual distribution of avian influenza A/H5 virus poultry outbreaks in each province of Vietnam from 2003-2010. Of note, Ha Tay province was incorporated in Hanoi in 2008.

**Supplementary Table 3**. Annual distribution of human cases of avian influenza A/H5 virus in each province of Vietnam from 2003-2010. Of note, Ha Tay province was incorporated in Hanoi in 2008.

**Supplementary Table 4**: Complete list of amino acid mutations identified at animal-human interface in Vietnam: 2003-2010. For each amino acid mutation, we indicated the residue number. The numbering found in the multiple sequence alignment used for analysis was based on A/Vietnam/1203/2004 as a reference. The table shows HA clade of the human virus, human strain name, human and avian amino acid names and their frequencies measured in the entire dataset, number of phylogenetically related human sequences with identical amino acid mutation, number of avian sequences phylogenetically related to the human sequence and collected before and after the human sequence.

**Supplementary Table 5**: Complete list of amino acid residues in the NA of Vietnamese H5N1 viruses previously associated with reduced susceptibility to NA inhibitor(s).

**Supplementary Figure 1A-H**: The PB2, PB1, PA, HA, NP, NA, M, and NS Bayesian trees ordered by time (x-axis) generated using the SRD06 codon model and uncorrelated lognormal clock model. Names of genetic lineages are shown on the right of the tree. The names of human H5N1 viruses are shown in red. Nodes are colored and sized based on posterior values (see legend for the color code). For HA and NA tree the age of the nodes and the rates for each branch are shown. For HA and NA genes, we show the amino acid changes occurring at each node of the major lineages and relative to the youngest sequence of that lineage (highlighted in yellow). The HA and NA reference sequences used to determine these amino acid changes are highlighted in yellow. For each HA sequence, we show on the right the region in Vietnam where they were collected. RRD-Red River Delta, NE- Northeastern, NW-Northwestern, NC-north coast, CH-central highlands, SCC-south central coast, SE-southeast, MRD-Mekong River Delta, UNK-unknown place of collection

**Supplementary Figure 2 A-H**: Bayesian skyline plots of PB2, PB1, PA, HA, NP, NA, M, and NS segments of HPAI H5N1viruses collected from Vietnam between 2003 and 2010. A measure of the relative genetic diversity is shown on the y-axis with the 95% highest posterior density (HPD) intervals shown in blue.