

 MILESTONE 7

Origin story

“ HIV-1 was circulating cryptically in Africa for generations



AIDS was first described as a new disease in 1981 (MILESTONE 1), and the causative lentivirus that came to be known as HIV-1 was identified a couple of years later (MILESTONE 2). However, the origins of HIV-1 and the reasons for its explosive appearance and rapid transformation into a global epidemic remained a mystery.

By the mid-1980s, evidence had accumulated that AIDS had been present in Central Africa considerably earlier than the first descriptions of the disease in the West. Therefore, the suspicion was that the HIV pandemic might have arisen from a related virus circulating in an animal reservoir in sub-Saharan Africa—but in which species?

The inklings of an answer began to emerge from two West African patients presenting with an antigenically distinct AIDS-causing virus that subsequently came to

be known as HIV-2 (MILESTONE 6). Genetically distant from HIV-1, HIV-2 was instead shown to be closely related to a lentivirus infecting an African monkey—the sooty mangabey. Subsequent studies confirmed that lentiviruses are endemic to many species of African monkeys and some apes—and these have collectively become known as simian immunodeficiency viruses (SIVs). Sooty mangabeys in particular were found to be naturally infected with a lentivirus known as SIV_{smm} (with the subscript indicating the name of the infected species), and genetic evidence showed that this virus was transmitted to humans, generating the HIV-2 epidemic.

HIV-2 is usually less pathogenic than HIV-1 and is far less common and widespread, being largely confined to a few West African countries. However, the AIDS pandemic that has led to more than 30 million deaths worldwide is overwhelmingly driven by HIV-1, and in particular the M group of HIV-1 strains. A key advance in nailing down the origin of HIV-1 was made in 1989 by Martine Peeters and colleagues. The study identified an SIV in wild chimpanzees (SIV_{cpz}) that was serologically identical to HIV-1 but not HIV-2. Soon after, work by Simon Wain-Hobson's group confirmed that SIV_{cpz} had a very similar genetic organization to HIV-1. Evidence was therefore stacking that SIV_{cpz} was the likely source of the HIV-1 pandemic, but the timing, and locale of its origin were unclear.

An important clue to the timing of the epidemic was found in 1998 by David Ho's group, who managed to amplify and partially sequence HIV-1 from a 1959 plasma sample—to date, the oldest known definitive case of HIV-1 infection. This pinpointed the infection to the area around what is now Kinshasa in the Democratic Republic of Congo. Indeed, it's now known that this region is where most of the early diversification of M group HIV-1 has occurred. Another

critical insight into the origins of the HIV-1 epidemic was made by Beatrice Hahn and colleagues in a 1999 paper. Studying wild-caught chimpanzees, this study combined SIV_{cpz} sequencing with mitochondrial DNA analysis to identify the infected chimpanzee subspecies. Used together, this information showed that two chimpanzee subspecies, *Pan troglodytes troglodytes* and *Pan troglodytes schweinfurthii*, hosted divergent SIV lineages—SIV_{cpzPtt} and SIV_{cpzPis}, respectively. Strikingly, all HIV-1 strains known at the time, including those in the pandemic M group, were closely related to SIV_{cpzPtt}, strongly suggesting that *P. t. troglodytes* served as the origin of the HIV-1 pandemic. This was subsequently confirmed by identifying natural *P. t. troglodytes* reservoirs of the HIV-1 precursor in southeastern Cameroon. Why SIV_{cpzPis} has been unsuccessful at jumping species into humans remains unknown but may be related to this virus's inability to overcome restriction factors in potential human hosts (MILESTONE 17). How SIV_{smm} and SIV_{cpzPtt} made the leap into humans is not entirely clear, but it's likely to have occurred via the unsafe consumption and preparation of bushmeat.

More recent molecular timing and modeling studies have pushed back the earliest appearance of M group HIV-1 to around the beginning of the twentieth century. This would suggest that HIV-1 was circulating cryptically in Africa for generations before factors such as urbanization and mass movement of people propelled it onto the global stage.

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ORIGINAL ARTICLES Peeters, M. et al. Isolation and partial characterization of an HIV-related virus occurring naturally in chimpanzees in Gabon. *AIDS* 3, 625–630 (1989) | Huet, T., Cheyner, R., Meyerhans, A., Roelants, G. & Wain-Hobson, S. Genetic organization of a chimpanzee lentivirus related to HIV-1. *Nature* 345, 356–359 (1990) | Zhu, T. et al. An African HIV-1 sequence from 1959 and implications for the origin of the pandemic. *Nature* 391, 594–597 (1998) | Gao, F. et al. Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. *Nature* 397, 436–441 (1999) | Korber, B. et al. Timing the ancestor of the HIV-1 pandemic strains. *Science* 288, 1789–1796 (2000) | Keele, B. F. et al. Chimpanzee reservoirs of pandemic and non-pandemic HIV-1. *Science* 313, 523–526 (2006)

FURTHER READING Sharp, P. M. & Hahn, B. H. Origins of HIV and the AIDS pandemic. *Cold Spring Harb. Perspect. Med.* 1, a006841 (2011)



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