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Zoonotic Potential of Simian Arteriviruses

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Wild nonhuman primates are immediate sources and long-term reservoirs of human pathogens. However, ethical and technical challenges have hampered the identification of novel blood-borne pathogens in these animals. We recently examined RNA viruses in plasma from wild African monkeys and discovered several novel, highly divergent viruses belonging to the family *Arteriviridae*. Close relatives of these viruses, including simian hemorrhagic fever virus, have caused sporadic outbreaks of viral hemorrhagic fever in captive macaque monkeys since the 1960s. However, arterivirus infection in wild nonhuman primates had not been described prior to 2011. The arteriviruses recently identified in wild monkeys have high sequence and host species diversity, maintain high viremia, and are prevalent in affected populations. Taken together, these features suggest that the simian arteriviruses may be “preemergent” zoonotic pathogens. If not, this would imply that biological characteristics of RNA viruses thought to facilitate zoonotic transmission may not, by themselves, be sufficient for such transmission to occur.

Novel human pathogens are emerging from wildlife at increasing rates (1, 2). Recent efforts to understand this phenomenon have focused on identifying microorganisms with zoonotic potential in their “preemergent” state, i.e., within their “natural” host(s) (1, 3). Even with advances in pathogen discovery technology, a complete global assessment of animal pathogens is not currently feasible (3). However, not all pathogens possess equal zoonotic potential. In particular, multihost pathogens and RNA viruses are significantly more likely to cause zoonoses than pathogens of other classes (4). Additionally, nonhuman primate hosts in Africa are historically important sources of zoonotic pathogens (5–8).

Recently, we used unbiased deep sequencing to identify and characterize RNA viruses in the plasma of African nonhuman primates. Our survey included 10 or more primates from populations representing eight cercopithecoid (i.e., Old World monkey) species. These samples were collected from multiple distinct geographic regions, spanning over 3,000 km. In nearly half of these populations, we discovered novel highly divergent viruses belonging to the family *Arteriviridae* (9–12) (Fig. 1). Along with coronaviruses, roniviruses, and mesoniviruses, arteriviruses belong to the order *Nidovirales* and infect a variety of mammals, including pigs, horses, mice, possums, and Old World monkeys (13). Notably, the arteriviruses are the only family of RNA viruses that infect mammals for which human infection has never been documented (14).

The arteriviruses that we discovered in wild African monkeys—here referred to as simian arteriviruses—are monophyletic, and all possess genomic features that indicate common ancestry with simian hemorrhagic fever virus (SHFV). These viruses all contain a duplication of 3 to 4 open reading frames (ORFs) in the 3′-proximal half of the genome that is not observed in other

arteriviruses (13). These additional ORFs putatively express additional structural proteins that are thought to be required for replication, but their precise function is not understood.

A history of cross-species transmission.

SHFV was identified in 1964 following an outbreak of simian hemorrhagic fever (SHF) which affected Asian macaques of several species (*Macaca fascicularis*, *Macaca mulatta*, and *Macaca arcuoides*) in a quarantine facility at the National Institutes of Health (NIH; Bethesda, MD) (15). Clinically, SHF is characterized by fever, facial edema, cyanosis, anorexia, adipsia, vomiting, dehydration, and signs of hemorrhagic disease (e.g., melena, petechiae, subcutaneous hematoma, retrobulbar hemorrhage, and epistaxis) (16). Internal hemorrhages affecting the lungs, liver, kidneys, and gastrointestinal tract are found on pathological examination (17). Laboratory tests from monkeys with SHF reveal hematologic and urinary changes characteristic of viral hemorrhagic fever (VHF) in humans, including lymphopenia with a left shift followed by neutrophilic leukocytosis, thrombocytopenia, prolonged coagulation time, and proteinuria indicative of renal failure (18). The case-fatality rate of SHFV infection in the 1964 NIH outbreak was initially reported to be 100%; however, this rate may be an over-

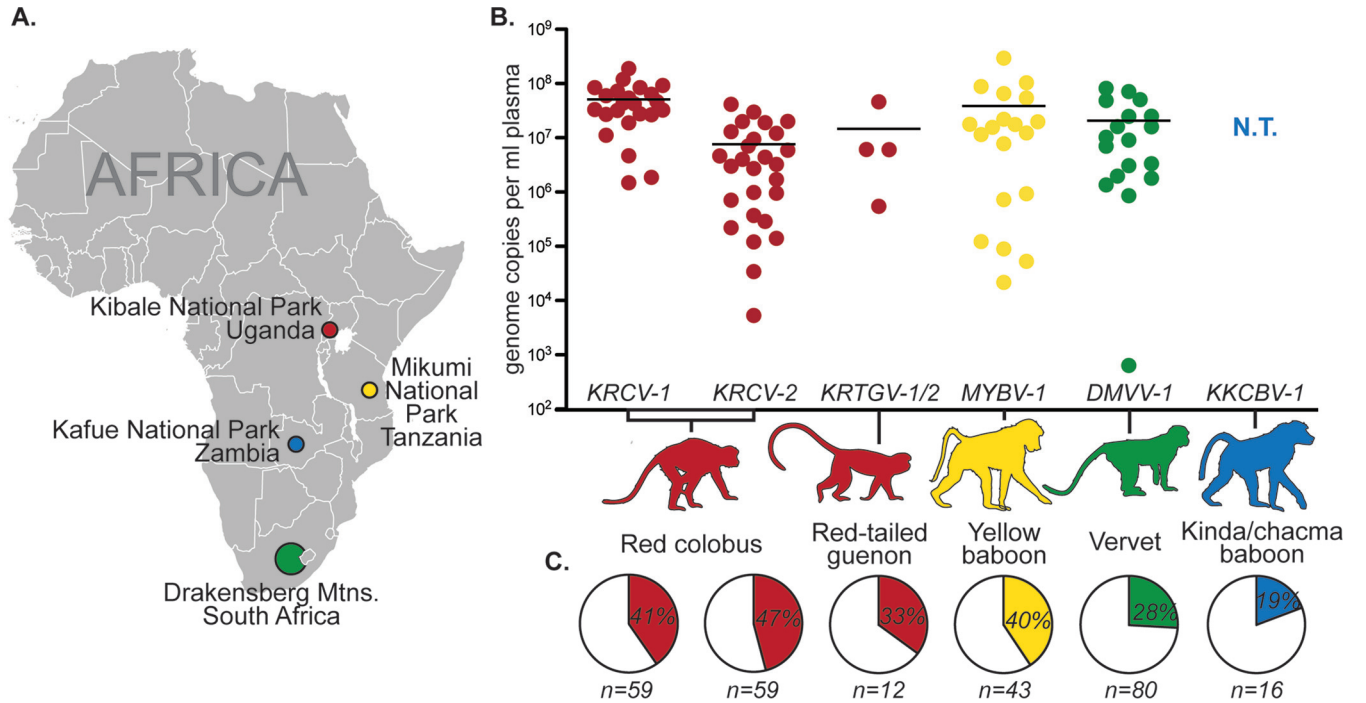
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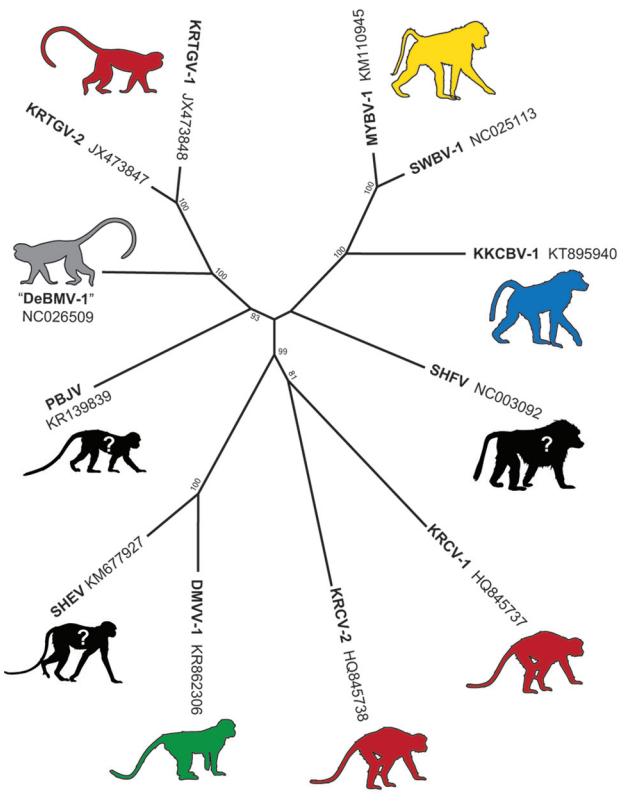
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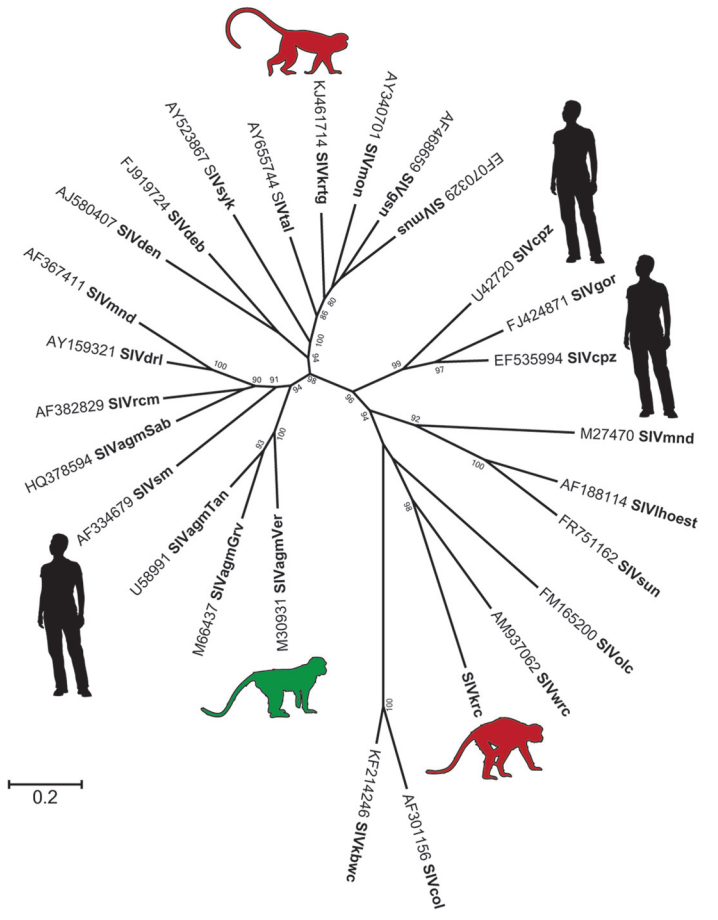
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D. Simian arteriviruses



E. Simian immunodeficiency virus



estimate as subclinical infection in a small number of individual macaques has since been documented (16). Additional outbreaks of SHF (affecting macaques of the species *M. fascicularis*, *Macaca nemestrina*, *M. mulatta*, and *Macaca radiata*) occurred throughout the 1960s to 1990s (19–23), with transmission among macaques occurring via direct contact and indirect contact and possibly via aerosol routes (24).

Although the source of virus in these outbreaks was never definitively identified, serological studies of captive African monkeys implicated primates of several species—namely, patas monkeys (*Erythrocebus patas*), grivets (*Chlorocebus aethiops*), and Guinea baboons (*Papio papio*)—as subclinical carriers and likely sources (24). However, captive patas monkeys inoculated experimentally with SHFV developed significant signs of disease (25), demonstrating that simian arterivirus-induced pathology is not specific to macaques. Moreover, although it was originally presumed that all SHF outbreaks were caused by a single agent (i.e., SHFV), we recently showed that at least three highly divergent simian arteriviruses were responsible for past outbreaks of SHF, suggesting that the simian arteriviruses as a group possess features that facilitate transmission among primates of different species (26).

Characteristics of natural simian arterivirus infection. Despite the widely held suspicion that African monkeys were the natural reservoir for SHFV, it was not until 2011 that the first SHFV-like viruses were discovered in a wild animal: a red colobus monkey (*Procolobus rufomitratus tephrosceles*) in Kibale National Park, Uganda (the viruses were referred to as KRCV-1 and KRCV-2, to indicate Kibale red colobus viruses 1 and 2, respectively) (11). We have since discovered simian arteriviruses in red-tailed guenons (*Cercopithecus ascanius schmidti*) from Kibale (Kibale red-tailed guenon viruses 1 and 2 [KRTGV-1 and -2], respectively) (12), yellow baboons (*Papio cynocephalus*) from Mikumi National Park in Tanzania (Mikumi yellow baboon virus 1 [MYBV-1]) (10), hybrid kinda × grayfooted-chacma baboons (*Papio kindae* × *Papio ursinus griseipes*) from Kafue National Park in Zambia (Kafue kinda-chacma baboon virus [KKCBV-1]), and vervets (*Chlorocebus pygerythrus*) from the Drakensberg Mountains in South Africa (Drakensberg Mountain vervet virus 1 [DMVV-1]) (Fig. 1A). These viruses were detected at high titers in the blood of infected individuals ($\approx 1 \times 10^7$ genome copies/ml [Fig. 1B]) and were prevalent in affected populations ($\approx 40\%$ of monkeys tested [Fig. 1C]). Sequence analysis revealed that simian arteriviruses from each species share only $\approx 50\%$ nucleotide identity with one another or SHFV (Fig. 1D). These discoveries also demonstrate that all major clades of cercopithecoid monkeys, including both recognized cercopithecoid subfamilies, naturally harbor simian arteriviruses.

Although simian arteriviruses have been identified to date in

monkeys from only four locations, the distribution of these sampling sites suggests that simian arterivirus infections occur in monkeys across sub-Saharan Africa. Alternatively, the lack of detection of simian arterivirus infection in black-and-white colobus monkeys (*Colobus guereza*) ($n = 10$) or olive baboons (*Papio anubis*) ($n = 23$) from Kibale, as well as sooty mangabeys (*Cercocebus atys*) ($n = 12$) from the Moa and Mabo rivers in Sierra Leone, implies that the occurrence of simian arterivirus infection in African monkey populations may be variable. Regardless, given the sequence, geographic, and host species diversity of these viruses in our limited data set—and that the natural host(s) of the viruses responsible for past outbreaks of SHF in macaques is still not known—many more simian arteriviruses are likely to be discovered.

Simian arterivirus biology and zoonotic potential. The zoonotic potential of a virus cannot be inferred from its biological properties alone. However, certain biological features are thought to potentiate zoonotic transmission of RNA viruses. These features include, but are not limited to, high genetic diversity, the ability to overcome host restriction factors, high virus production within infected animals, infection of primates, high prevalence of infection within naturally infected animal populations, and intense interactions between infected animals and humans (1, 27, 28). Although not all viruses known to be transmitted from animals to humans possess all of these features (7), various combinations of these characteristics are observed in RNA viruses that have emerged (or are emerging) to threaten human health.

Theoretically, high genetic diversity may facilitate cross-species transmission of a virus by providing a variety of phenotypically unique viral variants that may interact with host factors in different ways (27–29). Classically, phylogenetic analyses have been used to quantify the diversity of a virus (or group of viruses) at the family, genus, species, strain, or isolate level. At each of these levels, the simian arteriviruses display an impressive degree of diversity, even in comparison to simian immunodeficiency virus (SIV), a virus known for its high genetic diversity also found in African primates (Fig. 1E). Indeed, a motivating force behind newly proposed taxonomic revisions of the *Arteriviridae* has been the recent recognition of diversity within the simian arterivirus clade (30). Recent advances in sequencing technology have also allowed for detailed analysis of viral diversity within infected animals. The effect of this “intrahost” viral diversity on cross-species transmission is not yet well understood and warrants further investigation. Intuitively, one might expect that high viral diversity in the source host would increase the likelihood that one or more viral variants will be capable of replicating in the recipient host. In wild monkeys studied to date, simian arteriviruses display high levels of intrahost diversity (9). While it remains to be seen

FIG 1 Features of simian arterivirus infections among African monkeys. (A) Map of Africa depicting the geographic locations where wild monkeys harboring simian arteriviruses have been sampled. Colors correspond to the respective host species and virus throughout the figure. (Map from Lokal_Profil [<https://commons.wikimedia.org/wiki/File:BlankMap-Africa.svg>].) (B) Plasma viral loads, as measured by quantitative reverse transcription-PCR, showing simian arterivirus viremia in infected monkeys. N.T., not tested. (C) Prevalence of simian arterivirus-positive monkeys in affected populations, as determined by quantitative reverse transcription-PCR, reverse transcription-PCR, and/or unbiased deep sequencing. (D and E) Phylogeny of known simian arteriviruses (D) with a simian immunodeficiency virus (SIV) phylogeny shown on the same scale for comparison (E). Maximum likelihood trees were generated using MEGA6.06 (1,000 bootstrap replicates, GTR+I+ γ model) from codon-based alignments (via MAFFT) of 12 simian arterivirus ORF1b sequences or 27 simian immunodeficiency virus *gag* sequences. Bootstrap values of less than 70 are not shown. DeBMV-1, De Brazza's monkey virus 1; DMVV-1, Drakensberg Mountain vervet virus 1; KKCBV-1, Kafue kinda-chacma baboon virus 1; KRCV-1/2, Kibale red colobus virus 1/2; KRTGV-1/2, Kibale red-tailed guenon virus 1/2; MYBV-1, Mikumi yellow baboon virus 1; PBJV, Pebbah virus; SHEV, simian hemorrhagic encephalitis virus; SHFV, simian hemorrhagic fever virus; SWBV-1, Southwest baboon virus 1.

whether this diversity includes variants capable of establishing a successful infection in humans, it may increase the likelihood that such a simian arterivirus variant exists.

High virus production in naturally infected animal hosts may also facilitate cross-species transmission by increasing the dose of virus transferred to the recipient host. As the dose of virus required to initiate infection is influenced by the route of transmission and several variables intrinsic to the virus and host in question, direct comparisons between unrelated viruses are difficult. However, several zoonotic RNA viruses are known to have high viral loads in their natural hosts, e.g., lentiviruses in primates (31), hantaviruses in rodents (32), and coronaviruses in camelids (33). Although the route(s) by which simian arterivirus infections might be acquired by humans remains unknown, the high titers of virus detected in the blood of infected monkeys (Fig. 1B) suggest that even a small exposure to blood from an infected animal could expose a human to a relatively large quantity of virus. The extent and type of contact between humans and wild nonhuman primates in Africa vary by geographic region, local customs, and the specific primate species in question. However, many groups of humans come into contact with monkeys through hunting, butchering, and consuming bush meat, including primates from populations known to harbor simian arteriviruses (34–36).

The host factors that influence zoonosis are myriad and highly virus specific. Although host phylogenetic relatedness may serve as a rough proxy for susceptibility to cross-species viral infection, some RNA viruses (e.g., filoviruses, rhabdoviruses, and influenza A viruses) have a very broad species tropism while others (e.g., lentiviruses, hepaciviruses, and pegiviruses) appear to be highly host species restricted (37–40). African monkeys are more closely related to macaques than they are to humans (41), but the full extent of simian arterivirus species tropism remains an important open question. Identifying the specific cellular factors utilized by simian arteriviruses should allow for more sophisticated analyses of simian arterivirus infection in its hosts (42). Determining the host factors that influence simian arterivirus pathogenesis and disease severity in various hosts is another potentially valuable, yet unexplored, avenue of research.

Simian arteriviruses appear to cause persistent viremia in African monkeys, suggesting that these viruses may have evolved mechanisms to evade the immune system (9, 10), as has been shown for other, nonsimian arteriviruses (13). While persistence directly influences the prevalence of infection in a given population, preexisting immune evasion mechanisms might also play an important role in establishing infection in a novel host. We speculate that simian arterivirus persistence in natural hosts may be mediated, in part, by genetic plasticity and mutational escape of host immune responses, as has been shown for other persistent viruses such as HIV and hepatitis C virus (9, 43, 44). The ability of simian arteriviruses to cause persistent high-titer viremia and genomic diversity in their natural hosts does not guarantee that these properties would be maintained in zoonotic human infections. However, high-titer replication and genetic plasticity could also facilitate rapid adaptation to a human host, lowering barriers to replication in humans and human-to-human transmission.

A final consideration is the possible effect of simian arterivirus infection on the pathogenesis of other coinfections. For example, Reston virus, a relative of Ebola virus, was discovered during a particularly severe outbreak of SHF (45). Given the high prevalence of infectious diseases in human populations most likely to be

exposed to simian arteriviruses, there exists the possibility for synergy among coinfecting pathogens and simian arteriviruses.

Are simian arteriviruses a zoonotic threat? Our ability to identify viruses in nature and predict their emergence in humans is still in its infancy. Yet, given the features of simian arterivirus biology explored to date, investigation into the zoonotic potential of these viruses seems prudent. Importantly, lack of documented human infection should not be taken as evidence for lack of zoonotic potential. For example, if a human were infected with a simian arterivirus, would that infection cause clinical disease, and if so, would that disease be distinguishable from other, more common infections? Searching for evidence of simian arterivirus infection in people (e.g., animal caretakers and bush meat hunters) or wild great apes (e.g., chimpanzees and gorillas) that interact frequently with infected monkeys could help answer these questions. However, the genetic diversity of known simian arteriviruses (and presumably of those not yet discovered) poses a formidable technical barrier to such an analysis. For this reason, screening of additional primate populations will be essential to resolve the genetic diversity, host range, geographic distribution, and natural history of simian arteriviruses. Technologies such as unbiased deep sequencing will undoubtedly play a major role in this effort. As we gain a greater appreciation for the extent of simian arterivirus diversity, more widely accessible techniques (e.g., PCR and serology) may become useful in screening for simian arterivirus infections in humans.

The recent discovery of multiple highly diverse and prevalent simian arteriviruses in primates of several species across sub-Saharan Africa highlights how little we know about these viruses. Research on these viruses to date has identified the characteristics described here, but further characterization of the molecular biology, evolution, and ecology of these viruses is needed to more fully appreciate the implications of these viruses for human health. The relative rarity with which novel human pathogens emerge and the effectiveness of antiviral host restriction factors might suggest that the simian arteriviruses are unlikely to do so. However, understanding why certain viruses do not emerge in humans despite predisposing biological characteristics may also hold value for refining our understanding of the factors that drive zoonotic transmission of RNA viruses.

ETHICS STATEMENT

All research involving nonhuman primates was conducted according to the relevant national and international guidelines. Briefly, all animals were sedated prior to blood collection and were released back to their social group without incident following sample collection and recovery from anesthesia. All animal research was approved by the appropriate wildlife authorities and institutional animal care and use committees. Collection of samples from nonhuman primates in Uganda was approved by the Uganda Wildlife Authority (permit UWA/TDO/33/02), the Uganda National Council for Science and Technology (permit HS 364), and the University of Wisconsin Animal Care and Use Committee (protocol V01409-0-02-09) prior to initiation of the study, as described previously (11). Sampling of vervet monkeys in South Africa was approved by the Interfaculty Animal Ethics Committee (project no. 13/2010) at the University of the Free State and by the University of Wisconsin—Milwaukee Animal Care and Use Committee (protocol 07-08 #32) as described previously (31). Sampling of yellow baboons in Tanzania was performed in 1985 and

1986 using standard methods for field studies of baboons as described previously and was approved by the appropriate Tanzanian government authorities, Washington University, and Yale University. Sampling of hybrid kinda × grayfooted-chacma baboons in Zambia was performed in compliance with the rules of the Zambian Wildlife Authority and was conducted in compliance with the rules of the animal care and use committees from Baylor College of Medicine (AN-5538), Washington University School of Medicine (protocol 20120269), and New York University (protocol 10-1349) and applicable national laws.

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