

## MINIREVIEW

## Acute and Persistent Viral Life Strategies and Their Relationship to Emerging Diseases

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Most virologists would accept the concept that particular viruses often appear to have either acute or persistent patterns of host infection. The polyomaviruses of mammals, for example, uniformly establish persistent infections of a specific host. In contrast, it has recently become clear that avian polyomaviruses infect a broad array of bird species in an acute pattern (Lafferty *et al.*, 1999; Phalen *et al.*, 1999; Johnne and Muller, 1998). In this review, we develop the proposal that these two infection patterns define two life strategies of viruses with distinct evolutionary ecologies and consider the consequences on viral fitness and the ecological and evolutionary relationships. We suggest that persistent host-specific viral agents are the origin of emerging acute epidemic disease following adaptation of that virus to new host species.

The concept of life strategy for a species was first applied in an island biogeographical context where it appeared that specific organisms were better adapted either for initial habitat colonization (r-selected) or for long-term population equilibria (K-selected) (MacArthur and Wilson, 1967). We have previously considered if specific viruses might also exist with distinct life strategies. However, since various acute viruses can be both a virgin soil epidemic (r-selected) and a childhood infection at equilibrium in the population (K-selected), these life strategies cannot be applied to individual viral species (Villarreal, 1999). Yet viruses do appear to have distinct patterns of acute and persistent host infection. Viral persistence has been considered with respect to sources of epidemic disease (Mahy, 1985; Domingo *et al.*, 1998; Holland, 1996; Oldstone, 1998a). However, the term persistence can often include persistence of viral agents in host populations or in the environment [better termed viral durability (Cooper, 1985)]. To elucidate a

more specific relationship between the virus and individual host, in this review we limit the definition of persistence to only apply to viral persistence in an individual host.

The acute viral life strategy is a transient pattern of host infection in which the host immune response will eliminate or prevent the same virus infection from continued reproduction in that same host. Thus, these viruses must find a new host during the limited period of virus reproduction in order to continue their infectious cycle. This familiar life strategy applies to many human viral infections that are responsible for epidemic disease (smallpox, measles, poliovirus, influenza virus, rhinoviruses). These acute viruses have a high dependence on host population structure as described by the apparently accurate mathematical models that resemble predator-prey dynamics in which the viruses act as predators on their host prey (MacArthur and Wilson, 1967; Anderson and May, 1991).

Several distinct characteristics apply to acute viruses. They are often disease associated, show high mutation rates (in RNA viruses), can exist in genetically diverse quasi-species (Domingo and Holland, 1997; Domingo *et al.*, 1998; Domingo, 1998), and frequently appear able to replicate in more than one species. Acute viruses tend not to show cospeciation (phylogenetic congruence) with their hosts and are more frequently found in hosts that exist as congregational (herd, flock) populations. It has previously been postulated that acute and virulent viral disease must represent a newly infecting virus for the host since viral-induced host death will negatively affect host fitness and should consequently limit host availability (Dubos, 1965; Burnet and White, 1972). Therefore, older, more established viruses may be more benign to their host. More recent theoretical considerations, however, challenge this view (Ewald, 1994; Frank, 1996; Lipsitch *et al.*, 1996).

Highly virulent viral infections of large host populations do not seem to generally evolve from the acute to

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TABLE 1  
Biological Characteristics of Acute and Persistent Viral Life Strategy

Acute virus life strategy	Persistent virus life strategy
No persistence in individual host	Persistence in individual host
Often disease associated	Seldom cause acute disease, often inapparent
High mutation rates (RNA virus)	Genetically stable
Replication in more than one species	Highly species specific
Do not show cospeciation with host	Often show cospeciation with host
Transmission is horizontal	Transmission is often from parent to offsprings or sexual contact
High dependence on host population structure	Less dependent on host population structure
Seldom evolves to persistence	The source of emerging acute disease in new host species

the persistent state. The acute virus life strategy can be stable biologically and over an evolutionary time period. Examples abound in a broad range of host species. Lytic viruses of bacteria that encode DNA polymerase [T4 and T even phage (Kutter *et al.*, 1995)], chlorella-like viruses of microalgae (Reisser, 1993; Van Etten *et al.*, 1991), baculoviruses in most host insects (Cooper, 1985; Adams and McClintock, 1991; Du and Thiem, 1997), and the iridoviruses (cytoplasmic replicating DNA viruses) of fish species (Mao *et al.*, 1997; Tidona and Darai, 1997) all appear to have long been present as strictly acute agents that can sometimes infect a broad range of species and are seldom persistent or latent (Whittington *et al.*, 1997). Parallels can also be found in human viral infections such as influenza, measles, smallpox, rabies, and HIV-1, which have not evolved avirulent or persistent life strategies. However, their adaptation to reproduction in human hosts may be considered by some to be evolutionarily recent (Diamond, 1997; McNeill, 1976; Oldstone, 1998b).

Despite high prevalence in natural populations, persistent viral life strategy has not received much attention. Persistence is defined here as that state in an individual host that follows an initial period of productive infection and occurrence of an antiviral host response, in which the virus maintains the capacity for either continued or episodic reproduction in the same host at some future period. These viruses are not fully cleared by the host immune response. Our definition of persistence also includes the condition known as latency in which virus reproduction can be partially or completely suppressed for prolonged periods, but the capacity for reactivation is maintained.

Most DNA viruses adhere to the persistent life strategy including polyomavirus, papillomavirus, adenovirus, adeno-associated virus, TT virus, and the alpha, beta, and gamma herpesviruses. Many (but not all) natural retroviral infections also appear to fit this life strategy (e.g., foamy virus in old world primates). Some RNA viruses also adhere to this strategy in their natural host, such as hantavirus in various species of rodents (Feuer *et al.*, 1999; Abbott *et al.*, 1999), arenaviruses in various

rodents (Fulhorst *et al.*, 1999), and rhabdoviruses (*Lyssa virus*) in Pteropid bat species (Gould *et al.*, 1998). These persistent viruses are generally highly species specific and genetically stable and show phylogenetic congruence or cospeciation between virus and host genomes. The best-studied examples of viral–host phylogenetic congruence are the human papillomaviruses (Bernard, 1994; Bernard *et al.*, 1994; Ho *et al.*, 1993), human polyomaviruses (Sugimoto *et al.*, 1997; Guo *et al.*, 1998; Agostini *et al.*, 1997), rodent hantavirus (Monroe *et al.*, 1999; Morzunov *et al.*, 1998; Ksiazek *et al.*, 1997), and rodent arenaviruses (Bowen *et al.*, 1997). The herpes viruses also appear to exhibit virus–host phylogenetic congruence (McGeoch and Cook, 1994; McGeoch and Davison, 1999; Umene and Sakaoka, 1999).

Persistent viruses can be less dependent on host population structure and transmission is often from parent to offspring during episodic periods of virus reactivation or via sexual contact. The fitness of these agents includes a strong temporal component in that the virus has a very small probability of infecting a new host during any short time interval. Therefore, it must remain viable within its host for extended periods in order to maximize transmission probability (Villarreal, 1999; DeFilippis and Villarreal, 2000, manuscript submitted). These agents appear as commensals, exacting no apparent fitness cost on the host. However, some viruses have developed specific strategies that compel the infected host to maintain the viral genome. The polydnviruses of parasitoid wasp species which are produced along with the wasp larvae are an extreme example of this as these viruses are required to prevent the parasitized host from killing the wasp egg and thus are essential for wasp survival (Stoltz, 1993). The features of the acute and persistent viral life strategy are summarized in Table 1.

Because most acute viral epidemics are dependent on substantial host population densities, they would not be expected to be sustainable in small, isolated, or nongregarious species such as those of the hunter–gatherers, prevalent during much of early human evolution. Thus, with respect to humans, most acute viruses appear to

TABLE 2

Emergence of Hantavirus from a Persistent Virus in the Rodent Host to an Acute Virus in Humans

Rodent name <sup>a</sup> (common)	Subfam	Hantavirus persistent; rodent specific	Human disease	Human-to-human
Striped field mouse	M	Hantaan (HTN)	HFRS	na
Yellow-neck mouse	M	Dobrava-Belgrade (DOB)	HFRS	na
Norway rat	M	Seoul (SEO)	HFRS	na
Bank vole	A	Puumala (PUU)	HFRS	na
Deer mouse	S	Sin Nombre (SN)	HPS	na
White-footed mouse	S	New York (NY)	HPS	na
Cotton rat	S	Black Creek Canal (BCC)	HPS	na
Rice rat	S	Bayou (BAY)	HPS	na
Long-tailed pygmy rice rat	S	Andes (AND)	HPS	Yes <sup>b</sup>
Meadow vole	A	Prospect Hill (PH)	na	na
California vole	A	Isla Vista (ISLA)	na	na
Western harvest mouse	S	El Moro Canyon (ELMC)	na	na
Musk shrew	So	Thottapalayam (TPM)	na	na
Bandicoot rat	M	Thailand (THAI)	na	na

*Note.* HFRS is hemorrhagic fever with renal syndrome. HPS is hantavirus pulmonary syndrome. na, not associated with disease. Subfamilies: A, Arvicolinae; M, Murinae; S, Sigmodontinae; So, Soricidae.

<sup>a</sup> Data from Schmaljohn and Hjelle (1997) and Monroe *et al.* (1999).

<sup>b</sup> Reported person to person spread in El Bolsón, Argentina (Wells *et al.*, 1997).

have been acquired as stable population infections following the invention of agriculture and the establishment of denser and larger human populations (McNeill, 1976; Diamond, 1997; Oldstone, 1998b). We now present examples that argue that these acute epidemic agents originate from persistent infections of other hosts.

Influenza A is a strictly acute human virus which does not establish persistence and displays a high genetic variability in order to continually infect human populations that would otherwise have acquired herd antiviral immunity. Yet as noted by Webster *et al.* (1993), all 14 HA subtypes of influenza A appear to have originated following adaptation of a virus that infects aquatic bird populations. In contrast to human infection, infection of waterfowl results in a persistent and generally inapparent infection in the gut. This persistent virus maintains a surprising level of genetic homogeneity with few changes having been recorded in the past 67 years. Thus, it is likely that acute human influenza A represents a host species jump of a persisting viral agent of aquatic birds.

In humans, hantavirus (strains Sin Nombre, Black Creek Canal, Rio Segundo, etc.) can cause a fatal acute hemorrhagic fever with renal syndrome (Feuer *et al.*, 1999) or pulmonary disease. Hantavirus, however, has not fully adapted to host-host transmission in human populations as this is seldom observed (Wells *et al.*, 1997). The human host is a species jump for this virus. It is now clear that the natural hosts of hantaviruses are various rodent species (such as field mice, *Peromyscus maniculatus*) in which the virus establishes an inapparent persistent infection of kidneys and other tissues (for reviews, see Schmaljohn and Hjelle, 1997; and Monroe

*et al.*, 1999). Furthermore, although an RNA virus with potential for high mutation rates, hantavirus appears to be genetically stable in its natural host and phylogenetic trees of the viral and host genomes are often congruent, suggesting a long-term evolutionary relationship between them (Monroe *et al.*, 1999; Morzunov *et al.*, 1998; Ksiazek *et al.*, 1997). Table 2 outlines these general features of persistent hantavirus infection in their natural rodent host and that subset of hantavirus that has been established to jump species resulting in acute disease in human hosts as well as one established instance of human to human hantavirus transmission. Thus, the differential hantavirus host biology adheres to persistent and acute life strategies.

Other emerging acute human infections, although less well characterized, are likely to have emerged from a persistent but as yet unidentified specific host reservoir. Both the recent epidemic disease in domestic pigs in Indonesia (Albina, 1997) and the emergence of rhabdovirus (Lyssa virus) acute infections from various persistently infected bat species in Australia (Gould *et al.*, 1998) appear to fit this pattern. It has been proposed that bats, particularly solitary microchiropteran species, are the reservoir for the human-associated Ebola virus (Beer *et al.*, 1999; Breman *et al.*, 1999; Monath, 1999).

The above examples represent various persisting RNA viruses that have undergone species jumps and sometimes adapted to become strictly acute agents in a new host species. Few examples of species jumps by DNA viruses were presented, yet most families of DNA viruses establish persistent infections. In some cases, such as with mammalian polyomaviruses and papillomaviruses, examples of species jumps are absent. These viruses

are highly prevalent within and phylogenetically congruent with their specific host species and also highly tissue restricted. This specificity is mediated by host molecular determinants (host DNA polymerase–primase, host transcription factors, and other nuclear proteins, p53, PCNA, etc.) that are in addition to those needed by RNA viruses (translation, protein processing and transport, etc.) (Shadan and Villarreal, 1995). Such molecular constraints coupled with lower genome variability for DNA present too high of an adaptive hurdle for species jumps by these agents. However, as noted above, the avian polyomaviruses are exceptional in that they appear to cause infections associated mainly with acute disease and are also able to infect various different species (and orders) of birds (Lafferty *et al.*, 1999; Phalen *et al.*, 1999; Johnes and Muller, 1998). The avian polyomaviruses neither establish stable persistent infections nor are they phylogenetically congruent with their host; thus, they seem to be acute viral agents (Shadan and Villarreal, 1995). In addition, the regulatory T-Ag of avian polyomaviruses (which is important for species specificity) is much smaller than that of mammalian polyomaviruses, lacking various host-interacting domains (Pipas, 1992).

Various herpesviruses are known to sometimes jump species. Herpes B virus of chimpanzees which has established an inapparent persistent (latent) infection in chimpanzee can also jump species resulting in a fatal encephalitis in humans. Conversely, humans bearing active HSV-1 lip sores pose a risk of lethal infection to new world monkeys. A more recent and perhaps better documented example of this situation was reported by Richman *et al.* who describe a novel nonlethal herpesvirus that latently infects Asian elephants (*Elephas maximus*) (Richman *et al.*, 1999). When held in captivity next to African elephants (*Loxodonta africana*), the virus can and has jumped to this new species where it replicates as an acute agent, causing highly destructive and normally fatal infection of the heart and liver. A converse acute infection of latent African virus into Asian elephants may have also occurred. It is interesting that in this example the new acute host species is closely related to the species that is persistently infected.

Rabbit myxomavirus is another well-examined model of DNA virus–host interaction. The European rabbit (*Oryctolagus cuniculus*) was introduced into Australia and quickly became a pest species. Rabbit myxomavirus was then introduced as a biological control agent since it causes a highly virulent acute disease in the European rabbit. However, even following adaptation of the virus and host from the initial highly lethal infections to a less lethal disease, the myxoma infection in these European rabbits is still strictly acute and does not establish a persistent infection (Fenner and Ratcliffe, 1965; Bull, 1994). In contrast, the natural species for myxomavirus is the new world rabbit (*Sylvilagus* species) in which the virus established a persistent infection with a corre-

sponding relatively benign disease (Regnery and Miller, 1972).

The densovirus and parvovirus families of DNA virus are also able to exist as either persistent or acute viruses. In the aquaculture of shrimp, the densovirus white spot disease virus (WSDV) poses a most serious threat to the culture of tiger shrimp (*Penaeus monodon*) by causing virulent acute infections (Spann and Lester, 1997). However, in wild populations of the greasy black shrimp (*Metapenus ensis*), WSDV infections are inapparent and show no disease (Wang *et al.*, 1997). Thus, these wild shrimp can be sources of tiger shrimp disease. In mammals, parvoviruses can be either persistent species-specific infections, such as human AAV or mouse orphanvirus, or strictly acute infections that do not lead to persistence as characteristic of the carnivore parvoviruses (Parrish *et al.*, 1988, 1991; Parrish, 1993, 1997).

Chronic viral infections, such as hepatitis B virus (HBV) liver infections or human HIV-1 infections, may represent an intermediate and confusing state between acute and persistent strategies as we have defined them. As HBV (and woodchuck HV) transmission is noninsect blood born and infections are not generally prevalent (Summers *et al.*, 1978; Millman *et al.*, 1984; Dejean *et al.*, 1982; Roggendorf and Tolle, 1995), it is difficult to understand how HBV adapted to early human populations. Most human infections (80%) are acute and become resolved with only a minority establishing chronic infection. In contrast, the great majority of infections with other persisting DNA viruses result in persistent host infections. However, with the related avian hepatitis viruses (duck, goose, heron) (which have 60% identity to HBV) infections are highly prevalent, vertically transmitted, asymptomatic, and genetically stable (Mandart *et al.*, 1984; Sprengel *et al.*, 1988; Chang *et al.*, 1999). These characteristics seem to identify a persistent life strategy and suggest that they might have been the original source for the adaptive expansion of the woodchuck or human virus. A related explanation for the origin of human HIV-1 is also likely. Recent phylogenetic analysis strongly suggests that HIV-1 originated from a persistent and inapparent simian immunodeficiency virus (SIV) infection of chimpanzee (SIVcpz) and from sooty mangabeys (SIVsm) (Hahn *et al.*, 2000). In their natural host, SIV is prevalent, genetically stable, and clinically inapparent consistent with a persistent life strategy [like foamy virus (Schweizer *et al.*, 1999)]. Human HIV-1 seems to have resulted from an SIV species jump and establishment of human infection with ongoing chronic viral replication and disease.

As persisting inapparent viruses in highly specific hosts are of no clear medical, agricultural, or commercial interest, they are difficult to identify and survey. Yet it is clear that most species harbor persistent viral agents. Thus, we can expect that perturbed ecological interactions which increase contact between previously iso-

lated species (e.g., human encroachment into novel habitats) will increase the risk of exposure to a persisting agent and the possibility it might adapt to become an acute agent. For example, the juxtaposition of related but previously isolated species would be one such perturbation. In this regard, xenotransplanted tissues that are infected with persisting agents will tremendously facilitate transmission of those agents as new, possibly acute infections (for review, see Stoye *et al.*, 1998). Organs cultured from cloned or embryonic tissues could be a better source of such tissue as they can be screened for most viral families to exclude such a possibility. However, genetic parasites, such as endogenous retroviruses, are more difficult to eliminate and would pose some potential risk.

Most species jumps result in evolutionary dead ends since transmission as a persistent virus is seldom achieved and sustainable acute transmission is often not achieved in the new species. It would therefore seem wise to try to limit these initial infections in order to minimize the population and genetic variability of acute virus in the new dead end host and reduce the probability of acute viral adaptation to that host.

## ACKNOWLEDGMENTS

We thank E. Wagner for his useful comments on the manuscript. L.P.V. was supported by NIH Grant GM36605 and by the Research Unit on Animal Viruses at the University of California, Irvine.

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