Pathogen-pathogen interaction
A syndemic model of complex biosocial processes in disease

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There is growing awareness of the health implications of the fact that infectious agents often do not act independently; rather their disease potential is mediated in diverse and significant ways by their relationships with other pathogens. Pathogen-pathogen interaction (PPI), for example, impacts various virulence factors in human infection. Although still in its infancy, the study of PPI, a form of epidemiological synergism, is emerging as an important arena of new research and new understanding in health and clinical care. The aims of this paper are to: (1) draw attention to the role of PPI in human disease patterns; (2) present the syndemics model as a biosocial approach for examining the nature, pathways, contexts, and health implications of PPI and (3) suggest the utility of this approach to PPI. Toward these ends, this paper (a) reviews three case examples of alternative PPIs, (b) describes the development and key concepts and components of the syndemics model with specific reference to interacting infectious agents, (c) contextualizes this discussion with a brief review of broader syndemics disease processes (not necessarily involving infectious disease) and (d) comments on the research, treatment and prevention implications of syndemic interaction among pathogens.

Introduction

In the classic epidemiology triad, the clinical expression of infectious disease is understood as a product of an intricate relationship involving an infectious agent, the host's immune response, and environmental factors, including clinical management, that impact the overall health status of the host. More recently, with growing attention to both the evolutionary history of species and the importance of comorbidity in health, there has been growing interest in the fact that infectious agents often do not act independently; rather their disease potential is mediated in diverse ways by their relationships with other pathogens. Stress

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strains of the same pathogen, such as influenza... or dengue..., or interacting diseases such as HIV/AIDS and malaria..., at both the population and intrahost levels.” Of note, various virulence factors in human infection may be significantly influenced by such interplay. Although still in its infancy, the study of pathogen-pathogen interaction (PPI), a form of epidemiological synergism, is emerging as an important arena of new research and new understanding in health and clinical care.4

The aims of this paper are to: (1) draw attention to the role of PPI in human disease patterns; (2) present the syndemics model as a biosocial approach for examining the nature, pathways, contexts and health implications of PPI; and (3) suggest the utility of this approach to PPI in research, clinical and public health efforts. Toward these ends, this paper (a) reviews a series of case examples of PPI, including their dynamics and consequences, (b) describes the development and key concepts and components of the syndemics model with specific reference to the mechanisms of interaction among infectious agents, (c) contextualizes this discussion with a brief review of broader syndemics disease processes (not necessarily involving infectious disease), and (d) comments on the research, treatment and prevention implications of syndemic interaction among pathogens.

Case Examples of Pathogen-Pathogen Interaction

The list of identified PPIs that contribute to the health burden of human populations has grown rapidly in recent years.5 Examination of several case examples affords the opportunity to gauge similarities and differences in the pathways and outcomes of synergistic patterns in the diverse array of human pathogens. These cases were chosen because of the range of pathogens and the varying mechanisms and consequences of co-infection.

Amoeba/bacteria interaction. Awareness has been mounting for over 30 years of the role amoeba play in facilitating bacterial infection. In an initial report on Legionnaires’ disease, Rowbotham noted the capacity of Legionella pneumophila, the causal agent, to multiply intracellularly within amoeba and proposed that “an amoeba, full of legionellae, rather than free legionellae, could be the infective particle for man.”6 This idea was based on findings showing that both pathogens (i.e., free-living amoeba of the genus acanthamoeba, known to be a cause of keratitis and encephalitis) can cohabitate in water
cooling towers, evaporative condensers, and other manmade and natural water systems. While amoeba normally feed on bacteria, Rowbotham further reported that these bacteria survive inside amoeba, a finding that has been linked to the fact that the natural human targets of legionellae infection—macrophages and other phagocytic cells—are (evolutionary distant) amoeboid cells. In such cases, amoeba escape infection by the bacteria through encystment. Consequently, it has been suggested that adaptation to amoeba (i.e., “amoeba-resistance”) served evolutionarily as a pre-adaptation to the macrophage internal environment, an important step in the process of becoming a human pathogen.

Molecular evidence showing that related genes are required for the infectivity of both amoeba and macrophages was first provided by Cianciotto and Fields. These researchers argued that the macrophage infectivity potentiator gene (MIP) is active in bacterial resistance to intracellular killing within amoeba. Gao et al., later affirmed that intra-amoebal pre-adaptation to conditions within macrophages occurred at the molecular level. Specific genes involved in multiplication in both amoeba and macrophages have subsequently been identified as the \( ppr \) and \( icm \) loci (including both \( icmM \) and \( tphA \)). As Gao et al. remark, “Although the mechanisms of uptake of \( L. \) pneumophila by mammalian and protozoan cells are different...the similarity in the intracellular infections of macrophages and protozoa by \( L. \) pneumophila is quite remarkable.” Also similar are the life cycles of the bacteria within amoeba and macrophages.

Subsequent research suggests that under adverse environmental conditions the amoeba may for long periods offer a protective environment for the bacteria, and, as well, operate as a “Trojan horse” that inserts the bacteria into the human host. In an experimental animal model, this role has been demonstrated in the case of the water- and soil-dwelling \( M. \) avium by Cirillo et al. In the presence of amoeba, \( M. \) avium (which in humans is a common cause of systemic infection in patients with AIDS), was found to have greater ability to cross the murine intestinal epithelium and to complete intracellular replication than when amoeba were not present. Moreover, these researchers noted that amoeba-grown \( M. \) avium was more virulent than culture-grown bacteria. The protection afforded to bacteria by amoeba is revealed in the fact that they are found within cyst walls of the amoeba, sites that are quite resistant to excessive temperature, pH and osmolarity levels as well as biocide exposure. Additionally, as Miltner and Bermudez observe, “Enhanced resistance of \( M. \) avium to antimicrobials either by location within amoebae or by passage within amoebae may impact the efficacy of the prophylactic use of antimicrobials” like rifabutin and macrolides in eliminating infection.

Notably, as Greub and Raoult observe, “the virulence traits selected by intra-amoebal life... persist in the ‘species’ genome.” These traits, which enhance the pathogenicity of these bacteria relative to human macrophages, include: motility, an invasive phenotype, and resistance to cold, antibiotics (e.g., erythromycin), and biocides. The capacity for virulence in these bacteria as a human pathogens, in short, was honed independent of and no doubt long previous to contact with the internal environment of the human host.

Amoeba-resistance traits allow Legionella organisms to not only enter but to multiply within amoeba, a process affirmed by the identification of amoebal vacuoles that contain thousands of bacteria. To infect human hosts, however, the bacteria must exit the amoeba, a process that remains to be clarified but may involve expulsion or lysis. The latter, a pre-adaptation to human cell destruction, has been partially described and, notably, appears to be temperature dependent. Greub and Raoult suggest a possible scenario in which amoeba serve as bacterial reservoirs at lower temperatures, such as during initial body entry through the nasal mucosa and other first-line body defenses, followed by lysis and dispersal of the bacteria at the higher temperatures that are found in the human lower respiratory tract.

There is, in turn, some evidence that the development of amoeba-resistance in bacteria may enhance the pathogenicity of amoeba. Mendoza-Macias et al. for example, found in the case of \( E. \) coli 055 that activities of the bacteria significantly support amoebic grow and virulence. In other words, the impact of the interaction may be bi-directional with both pathogens gaining virulence through their interaction. From an intervention standpoint, the relationship of \( L. \) pneumophila with amoeba may help explain why it is difficult to clear water systems of the bacteria.

Acanthamoeba is now known to serve as a reservoir for various other pathogenic bacteria as well, including \( E. \) coli, \( C. \) burnetii, \( V. \) cholerae, \( P. \) aeruginosa and \( M. \) avium among others. In the case of \( E. \) coli, a major pathogenic cause of enteric/diarrhal diseases, various studies by Jung and co-workers suggest a complex array of exchanges and outcomes dependent on bacterial strain. Thus they note: “\( E. \) coli K1 interactions with Acanthamoeba are parasitic in nature while Acanthamoeba are potent predators of \( E. \) coli K-12, and the outcome of these convoluted interactions may be beneficial to Acanthamoeba or \( E. \) coli or may result in the development of a symbiotic relationship.” Most importantly, their research suggests that as with \( L. \) pneumophila, the amoeba has the ability to serve as a reservoir and Trojan horse for \( E. \) coli, roles regulated by the virulence properties of the evasive K1 strains of the bacteria. Acanthamoeba interaction in extracellular contexts occurs as well. Thus, Laskowski-Arce and Orth report on interaction between Acanthamoeba castellanii and the bacterium Vibrio parahaemolyticus. They found that while A. castellani does not prey on V. parahaemolyticus it secretes a substance that promotes the survival of the bacteria in coculture, suggesting an as yet unexplained potential contribution by an amoeba to a bacteria in the wild environment.

PPI involving amoeba do not appear to be limited to relations with bacteria as examples are beginning to be seen involving viruses (e.g., polioviruses, enteroviruses, mimiviruses, coxsackieviruses) as well. In the case of enteroviruses, for example, work by Danes and Cerva suggests the importance of Acanthamoeba castellanii as a transport vehicle that facilitates viral spread.

While at the micro-level, it is clear that amoeba can play a role in the spread of bacterial diseases like Legionnaire’s disease, social factors also appear to be at play in defining risk of infection. Risk in this instance is shaped by two factors: the presence and number of legionellae that reach people and the immunostatus of...
those the bacteria reaches. While Legionnaire’s disease outbreaks have occurred in various settings, poor and working people may be at special risk, both because of spending time in settings in which facilities may not be properly maintained and because of their generally poorer health status compared to wealthier social strata. While Legionnaire’s disease outbreaks have been reported in many settings, indoors and outdoors, there has been an increase over time at factories including automotive plants, plants that cool molded plastics with water, food manufacturers, soap factories, and waste-water treatment facilities, and at prisons, settings disproportionately populated by the poor and working classes. The increase in Legionnaire’s disease among working people in industrial settings and those who are incarcerated suggests the importance of considering both biological and social relations in PPI, including sociopolitical issues in the establishment of occupational health and safety regulation and enforcement.

HIV/HCV and HIV/fungal interactions. The appearance in 1981 of HIV/AIDS significantly magnified awareness of the profound clinical implications of PPI. Over the last several decades, it has become apparent that HIV works together with a wide range of other pathogens and that such interactions have helped to shape the global mosaic of the AIDS pandemic. From ancient scourges like malaria and tuberculosis to emergent diseases like hemoplasma infection and cat-scratch disease, HIV has been found to interact adversely with a host of infectious agents. Among diagnosed patients with HIV/AIDS, a notably common co-infection involves hepatitis C virus (HCV). In the United States, a quarter of a million people, or about 25–30% of HIV-infected individuals and 8% of HCV infected individuals, are co-infected with HIV-1 and HCV. A similar pattern is found in Europe. Overall, it is estimated that worldwide as many as 10 million people suffer HIV/HCV comorbid infection. Co-infection is particularly common in the Asia-Pacific region.

In most cases, dually infected individuals are current or former injection drug users (IDUs). In this population, HCV has proved to spread much more rapidly than HIV, often during the initial period of illicit injection as neophyte injectors are being taught by more experienced users how to inject into a vein. Multiple-person syringe use (commonly referred to as “syringe sharing” in the literature) is the most common route of spread for HCV. Research on accidental needlesticks among health care providers has shown that HCV has a rate of transmissibility that is ten times that of HIV. Ease of transmission and the large reservoir of HCV in the IDU population (rising to over 90% in some locations) explains why new IDU HIV/AIDS patients often have already been infected with HCV.

Both HIV and HCV are rapidly replicating (at the rate of 9.3 log10–10.2 log10 for HIV and 11.6 log10–13.0 log10 for HCV) single-stranded RNA viruses; they both cause chronic subclinical infection that can persist for many years prior to appearance of noticeable and potentially lethal symptoms; and both are transmitted through blood-to-blood contact and exchange. Despite these similarities, there also are important differences between HIV and HCV. Unlike HIV, HCV does not integrate into the nuclei of human cells, does not have a nuclear phase in its replication cycle, at least double the number of people infected with HCV alone are able to clear the virus without consequence compared to HIV clearance, and HCV is not readily transmitted through sexual contact (unless a person is already immunocompromised). In western countries, liver disease is the second leading cause of death among people with HIV/AIDS and hepatitis C virus infection causes the majority of cases of liver disease in these populations. Existing research indicates that HIV infection leads to hepatitis infections that are more aggressive than those in individuals not infected with HIV (although effects in the reverse direction—HCV on HIV—are less clear and may be unidirectional). HIV infection in a person with hepatitis C is associated with higher levels of the hepatitis C virus in the bloodstream, more rapid progression to liver disease, and increased rates of both cirrhosis and liver cancer. These negative health outcomes appear to be the consequence of the inability of the immune system to contain HCV after infection with HIV. Moreover, as Butt et al. found in their study comparing HIV-infected and uninfected HCV patients, “Although HIV infection itself is not associated with increased risk of diabetes, increasing age, HCV coinfection, and BMI have a more profound effect upon the risk of diabetes among HCV-infected persons.” As yet these researchers have not determined whether HIV and HCV act synergistically at the cellular level or through other factors in increasing diabetes risk. These findings have been affirmed by a large retrospective observational cohort study that showed that biopsy-proven co-infected HIV/HCV patients experience heightened rates of membranoproliferative glomerulonephritis, acute interstitial nephritis and acute tubular necrosis.

Additionally, HCV and HIV coinfection burdens the treatment process because dually infected individuals exhibit poor response to pegylated interferon (IFN) and ribavirin. Further, some anti-HIV medications are hepatotoxic in people suffering from liver damage due to chronic hepatitis. Moreover, drugs used to treat HIV and hepatitis can interact, producing undesirable side effects.

The precise mechanisms and pathways of HIV/HCV interaction remain to be clarified. There is growing evidence that the critical junction in the interaction lies in the adverse effects of HIV on CD4 cells, as suggested by the fact that HIV-infected individuals who do not produce HCV antibodies upon exposure have comparatively lower CD4 cell counts than HIV-infected individuals who produce HCV antibodies. There is also a suggestion emerging from various studies that HIV may assist HCV replication, although this is far from a universally held perspective. Other studies indicate that HIV and HCV viremia upregulate genes involved in immune activation and immunoregulatory pathways. Additionally, HCV infection is associated with aberrations in all peripheral immune cells, suggesting a global effect of HCV on the immune system which may facilitate HIV activation. Overall it is clear that the interaction of HIV and HCV has significant health consequences.

Of course, HIV interacts with many other pathogens besides HCV. The incidence, for instance, of invasive fungal infection has been climbing since the appearance of HIV/AIDS and consequent increase in the number of individuals that are
immunocompromised. Individuals with weakened immune defenses have proven to be particularly at risk for infection by fungal agents in the surrounding environment. Asperillus, for example, is a ubiquitous fungus known to colonize pulmonary cavities in tuberculosis patients, leading to the development of aspergilloma. Addrizzo-Harris et al. described the risks of asperillus/HIV coinfection based on 25 diagnosed cases of aspergilloma, 10 of whom were HIV-positive and 15 HIV-negative. Commonly, aspergillomas remain stable over time without treatment, but the condition can lead to potentially lethal coughing up blood or blood-stained sputum in some patients. In the comparative study, Addrizzo-Harris et al. found progression to a more invasive form of pulmonary aspergilloma among HIV-positive individuals with low CD4+ cell counts despite antifungal therapy. This finding is of note because of the prolonged survival of HIV/AIDS patients with significantly compromised immune systems and the increasing frequency of pulmonary aspergillosis and haemoptysis in these patients.

Notably, just as HIV is interactive with many different pathogens, including fungal pathogens, the latter are interactive with pathogens other than HIV. Candida albicans, a common yeast, for example, causes severe secondary infections in patients with tuberculosis. As Naz and Tariq indicate, “It has also been observed that secondary fungal infections in the lungs of pulmonary tuberculous patients are associated with marked cough, expectoration, dyspnea, fever, anaemia, leucocytosis and raised ESR.”

**Tick-borne disease interactions.** Tick-transmitted infections are the most common vector-borne diseases in the United States. In recent years, there have been significant increases in outbreak breaks of tick-borne diseases in several parts of the country. Most attention has been directed at Lyme disease, which is caused by several species of spirochetal Borrelia bacterium. Lyme disease is recognized as the most frequent tick-borne disease in North America and Europe, as well as one of the most rapidly spreading infectious diseases in the United States (with over 20,000 cases a year nationally since the turn of the 21st century and over 30 cases per 100,000 persons in the ten most heavily infested states). Furthermore, it has been established that the Ixodes ticks (frequently referred to as deer ticks) that transmit Borrelia burgdorferi, the identified causal agent of Lyme disease, often carry and can simultaneously transmit several additional human pathogens. These include both *Anaplasma phagocytophilum*, the bacterial cause of human granulocytic anaplasmosis, a disease that like HIV/AIDS appears to damage the immune system in a way that promotes opportunistic infection, and *Babesia microti*, a protozoan parasite that can trigger a malaria-like disease known as babesiosis. Additionally, Ixodes ticks are known to transmit the Powassan virus. This pathogen, which derives its name from the Canadian town of Powassan, Ontario, has been associated with a small number of cases of encephalitis. Similarly, in both Europe and Asia, Ixodes ticks transmit additional encephalitis-causing viruses. Co-inhabitation of ticks by several human pathogens has been observed in the laboratory and in one field study of tick populations over 70% were found to be co-infected with *B. burgdorferi* and *B. microti*. Further, immunoserologic testing affirms that comorbid human infection with more than one tick-borne pathogen occurs.

Several human studies indicate that co-infection with human granulocytic anaplasmosis increases the severity of Lyme disease. As Mitchell et al. point out, “Coinfection may explain the variable manifestations sometimes seen in patients with Lyme borreliosis, babesiosis and ehrlichiosis.” However, much remains to be learned about the pathways of tick-borne disease interactions and the precise nature of the health consequences of these interacting diseases. Heightened disease progression or other indications of adversity cannot be assumed. Thus, when mice were experimentally co-infected with *B. microti* and *B. burgdorferi*, no increased pathogenesis was observed as revealed by a range of measures, including pathogenic load, spleen weight and blood chemistry. Instead, both diseases developed along their normal course of infection causing the expected symptoms specific to each disease. Similarly, Krause et al. evaluated 192 patients with confirmed tick-borne infections and found that 39% presented with concurrent infections; 81% were co-infected with Lyme disease and babesiosis. The common symptom triad of fever, chills and headache was observed in 44% of the patients with Lyme disease and a co-infection compared with just 13% with Lyme disease alone. However, other adverse and more significant health outcomes seen in sufferers of tick-borne infections, such as arthritis, Bell’s palsy, meningitis and carditis, were equally distributed between patients with Lyme disease alone and those with Lyme disease and concurrent infection with another tick-transmitted disease. These findings suggest that coinfection infection may not increase the likelihood of acute dissemination of *B. burgdorferi*. In short, mere co-infection with two or more pathogens does not mean that adverse synergistic interaction will occur. Indeed, PPI can, in some cases, as seen during the early years of the 20th century in the impact of *Bordetella pertussis* (whooping cough) epidemics in reducing the transmission of measles in the UK, produce desirable health outcomes.

**Patterns of Pathogens in Interaction**

As this review of several specific cases suggests, pathogens can have significant impact upon each other, sometimes directly but at other times through the changes they cause to particular body systems and processes, including various layers and components of the immune system. Several pathways or types of interaction are described below. This categorization serves heuristically as a means of assessing some of the range of known pathogen interactions. As PPI research advances new forms of interaction are likely to be identified. Additionally, in any particular case of PPI two or more forms of interaction often occur, underlining the heuristic nature of this framework.

**Mobility support.** In the first type of disease interaction, one disease promotes the contagiousness of another disease by helping it to enter and gain access to vulnerable areas of the body. This type of interaction was described above in the case of Trojan Horse relationship of amoebas to bacteria in the spread of Legionnaire’s disease. An alternative type of mobility support is provided by hepatitis B (HBV) to hepatitis D (HDV), which is the...
smallest known infectious virus. First identified in 1977, HDV is a partial virus or satellite that lacks the ability to survive independently of HBV. The outer coat of HBV facilitates the attachment of HDV to host liver cells. Additionally, proteins on the HBV envelope facilitate the process of HDV replication by enabling the re-assembly of the HDV genome into new viral particles. The finally assembly, however, occurs independent of HBV, although it is dependent upon proteins drawn from the host cell.

It is estimated that approximately 300 million people worldwide suffer HBV infection. Of these, about 15 million also are infected with HDV. There are important regional differences in the frequency of HDV. The general population of the western portion of the Amazon Basin in Brazil has emerged as an endemic zone for HDV. The disease is also found in Mediterranean countries, sub-Saharan Africa, the Middle East; by contrast, in the United States, HDV infection is primarily limited to specific subpopulations including injection drug users and hemophiliacs.

Triple hepatitis infection (with HCV as well) has been identified in Mongolia, Taiwan and elsewhere. When HDV and HBV are both present, infection tends to be more severe leading to the development of chronic liver disease. In chronically ill patients (those in whom the virus persists longer than six months), the combined viruses cause inflammation throughout the liver, ultimately destroying liver cells, which are then replaced by scar tissue (fibrosis).

Enhanced contagiousness. A second form of PPI is seen in the type of interaction that occurs between the spirochetal bacterium Treponema pallidum that causes syphilis and HIV. A meta-analysis of 30 studies on dual infection found that the median HIV seroprevalence among individuals infected with syphilis was 15.7%, with 27.5% among men and 12.4% among women, indicating that HIV seroprevalence is high among patients with syphilis in the United States. High rates of co-infection are facilitated by the disruption of the multilayered epithelial barrier and genital-tract ulceration caused by syphilis which supports the sexual transmission of HIV. What is more, while oral sexual contact normally is a comparatively low risk behavior for HIV, oral syphilitic lesions recruit HIV target cells, increasing the risk for HIV transmission with repeated unprotected exposures. As a result of these factors, people with syphilis are two to five times more likely to transmit or contract HIV than are those who are infected with a sexually transmitted disease.

A number of adverse health effects of this pathogenic interaction also have been demonstrated, including presentation with multiple or deeper chancres and overlap of primary- and secondary-stage features of syphilis in coinfected individuals. In a coinfection study, Rompalo et al. found that “HIV infection had a small effect on the clinical manifestations of primary and secondary syphilis. Compared with HIV-uninfected patients, HIV-infected patients with primary syphilis tended to present more frequently with multiple ulcers, and HIV-infected patients with secondary syphilis presented with concomitant genital ulcers more frequently.” Atypical serologic responses have been reported in dually infected individuals, mostly involving higher than expected serologic titers. As with other infections in HIV patients, early syphilis may contribute to a decrease in CD4 cell levels and an increase in HIV RNA in plasma and semen, although evidence for these effects is not uniform. Most notably, in the presence of HIV it has been shown that there can be rapid progression from early syphilis to neurosyphilis resulting in blindness, loss of hearing, and paralysis.

Accelerated virulence. A third type of interaction between pathogens involves acceleration of virulence. This has been seen in several of the previously cited examples and is further exemplified in individuals that are coinfected with HIV and HSV (herpes). Several pathways have been described through which HSV-1 and HSV-2 could impact the life cycle of HIV-1, including a direct effect of herpes virus gene products on the transcriptional and post-transcriptional regulation of the HIV-1 provirus, an indirect stimulation of HIV-1 expression (facilitated by cytokine release), and an alteration of the HIV-1 cell tropism as the result of phenotypic mixing between the two pathogens.

In dually infected individuals, a significant degree of speeding up of AIDS pathogenesis has been described. As Palù et al. indicates, genital herpes, more than any other sexually transmitted disease, appears to be linked to HIV-1 transmission not only by boosting HIV-1 load, but also by providing a portal for entry and exit of the virus.” This increase appears to be caused by the specific effects that the herpes virus has on the pace of HIV viral replication. Various factors may be involved in this process, including specific herpes proteins (e.g., ICP-0, ICP-4 and ICP-27) that boost HIV replication efficacy.

Alterations of the physical body. Fourth, in some cases alterations of the body caused by one pathogen promote the disease progression caused by another pathogen. These alterations include changes in biochemistry (for example, damage or modulation of immune system components), cellular signaling capacity, and the integrity of organ systems. The case of herpes, and the production of genital lesions, noted above, is an example of this route of PPI. Another example involves interaction between tuberculosis and infection with the fungus Aspergillus fumigatus. The latter often colonizes residual cavities in the upper lobes of the lung caused by prior pulmonary tuberculosis or other lung infections. Within these cavities, which offer protection of the fungus, proliferating masses called fungus balls are free to develop.

Gene assortment. A final type of pathogen interaction is gene assortment, involving both the movement of genes from one strain or subtype of a microorganism to another strain and the movement across species (e.g., one bacterial species to another) or even across types of microorganisms (e.g., from a bacteria to a virus). HIV is regularly involved in the first type of gene assortment. Stemming from the high error rate of its reverse transcriptase replication method this species is characterized by a comparatively high mutation rate, resulting in the development of multiple viable (and unviable) strains representing somewhat distinct local viral lineages. Circulating recombinant forms of HIV are the products of coinfection with two or more strains at the cellular level and subsequent gene mixing. Rousseau et al. report gene mixing to be quite common in the subtype C strain of HIV in KwaZulu-Natal province, South Africa. Gene movement of this sort has had a significant impact on the evolutionary history of this pathogen, including enhancing the overall virulence of
in the sense that they are not completely separable phenomena. And overlapping threats to the health are not with men in the US “epidemic.”

factors, as seen in the importance of IDUs or men who have sex experienced and sustained by broader socioeconomic and behavioral linked diseases, in turn, and HIV/AIDS itself are strongly influenced and sustained by broader socioeconomic and behavioral contexts in which it occurs. As indicated by the Centers for Disease Control and Prevention, “research protocols, prevention programs, policy interventions, and other aspects of public health practice have focused on one disease at a time, leaving other health problems to be addressed by parallel enterprises.”

Alternately, it is possible to look at disease in terms of “processes, relationships—things together,” a perspective that has gained attention in biology in recent years. This alternative approach emerged, in part, because of the appearance in 1981 of HIV/AIDS and especially by its swift and disproportionate spread in the United States (and elsewhere) among the poor or other marginalized populations. In time, it has become clear that even standard public health terms like epidemic and pandemic, which are used to describe the sudden spread of HIV/AIDS locally and globally, do not adequately describe the real nature of HIV/AIDS as a disease process, which everywhere is closely entwined with a wide range of opportunistic infections and in certain populations involves transmission in close conjunction and consequential interaction with other, non-opportunistic, infectious and noninfectious disease and health conditions (such as tuberculosis, sexually transmitted diseases, hepatitis, malaria, cirrhosis, malnutrition, drug abuse and so forth). Many of these linked diseases, in turn, and HIV/AIDS itself are strongly influenced and sustained by broader socioeconomic and behavioral factors, as seen in the importance of IDUs or men who have sex with men in the US “epidemic.”

From the emergent syndemics perspective, broadly distributed and overlapping threats to the health are not concurrent epidemics in the sense that they are not completely separable phenomena. Rather they emerge disproportionately and tend to cluster among certain populations, especially those made vulnerable by social conditions. A syndemic, in short, involves a set of enmeshed and mutually enhancing health problems that, working together in a context of deleterious social and physical conditions that increase vulnerability, significantly affect the overall disease status of a population. As emphasized by King et al. in a discussion of people living with HIV/AIDS, “Treating [disadvantaged] persons with multiple diagnoses… is complicated—not only because of [both] independent and synergistic disease processes but also because of disparate access to care, limited or no insurance, and unmet subsistence needs…” Consequential disease interaction includes but is not limited to PPI, as it involves interplay among infectious agents, between infectious agents and biological and other mechanisms underlying non-infectious diseases, and between non-infectious disease and other health conditions. Moreover, this perspective moves beyond focus on the specific mechanisms of disease interaction to the interaction between disease and social conditions and the recognition that disease causation, progression, and cure cannot be viewed in solely biological terms. Research over the last decade has shown that syndemics, which have played a critical role in human disease history, are having a significant impact on diverse populations currently, and are likely to have continued consequential influence on the health profile of the emerging 21st century.

In short, syndemic research focuses simultaneously on distal and proximal causes of disease, specific mechanisms and directionalities of interaction, broader patterns and contexts of vulnerability and risk, and consequences of disease synergies that increase the overall health burden of a population. Central to this approach is the development of a systemic biosocial understanding of disease. As a result of its broad scope, syndemic research benefits from multidisciplinary collaboration. Key conjunctures of collaboration are illustrated in Figure 1 by the boundaries of specific areas of work, although, because commonly there is more than one discipline focused on specific aspects of the scope of work within each box multiple additional points of collaboration are evident.

Clinical and Public Health Implications

It is the perspective of this assessment that, as Nichter has suggested, “What is appealing about a syndemic approach… is both its explicit emphasis on examining connections between health and [society] and its attention to routes of transmission that affect clusters of interrelated health problems.” In other words, addressing syndemics requires public health, biomedical and health development models to move beyond individual risk, individual diseases and individual behavior change models to focus on relationships, contexts and processes. Addressing the HIV and malaria syndemic, a significant threat in malarial areas of Africa and Asia, for example, Abu-Raddad and Kublin observe, “The synergy between HIV and other diseases such as malaria provides us with more opportunities to combat HIV/AIDS by treating its co-infections with these other diseases.”

The syndemics approach underlines the fact that global public health challenges require comprehensive and multi-dimensional responses that embrace “the idea that the focal mission of public health goes beyond epidemic control to include improvements in the public’s health.” As emphasized by a holistic but theoretically focused syndemic perspective, this means advancing past narrowly conceived efforts toward an understanding of the
broader, socially and environmentally contextualized epidemiological patterns of a specific disease in order to prevent or control it and, further, moving toward the development of a response strategy that prioritizes the identification and assessment of disease clusters, investigates patterns of disease interactions, identifies addressable contextual factors that promote syndemic development, and recognizes the diagnostic and treatment challenges of interacting diseases and their agents. For example, detecting HCV in people who are immunocompromised by HIV infection can be difficult because they may not produce an antibody response sufficient to be detected with the existing HCV blood test. In HIV-positive people with a CD4 count below 200 cells/μl, an HCV RNA viral load test may be necessary to diagnose hepatitis C. Moreover, complex treatment issues arise in patients requiring the multiple antiviral therapies. These are magnified by findings suggesting group differences in response to PPI and to combined therapeutic regimes that remain to be fully elucidated.96-98

Emergent diseases, many of zoonotic origin (e.g., HIV, SARS, influenza) affirm as well the importance of breaking down the barriers that have separated the study of human and animal health. Monitoring of infectious disease emergence and spread in animals, for example, must be recognized as a potential critical component protecting human health, following the “one disease” model that has emerged in veterinary medicine.99-101

Age can also be a complicating factor in syndemics. The diagnosis of TB in children, for example, has always been difficult and is further compounded by co-infection with HIV. There are notable similarities in the clinic symptoms of these two and radiological changes may be non-specific. Treatment is further complicated by drug interactions and problems with adherence.102 In a study of patients over 50 years of age co-infected with HIV and HCV, Siegel et al.103 found that co-infection influences patient perception of and management of each disease, overall health status, and self conception. Participants were often confused about which disease to attribute particular symptoms and treatments, uncertainty that it was difficult for health care providers to effectively address. Further, treatment decisions were burdened by participants’ fear of liver damage from HIV medications, the uncertain efficacy and anticipated side-effects of HCV therapies, and the social stigmas attached to both diseases, leading to hopelessness regarding the future and anticipation of a shortened life expectancy as a result of dual diagnosis. In some settings, community response to specific diseases and to comorbidity can have significant impact on patient well-being. Thus a major challenge is to link medical efforts with strategies to combat the social stigma attached to these diseases.

These issues affirm the importance of a biosocial syndemic approach that considers the interplay among sociocultural and demographic factors, patterns and pathways of pathogen interaction, and recommended standards of care for comorbid conditions.

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Legionella pneumophila

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Figure 1. Components of PPI Syndemics and Conjunctures of Multidisciplinary Interaction.
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