Perspective

What Can We Learn From Measles? No New HIV Infections

Reducing the incidence of HIV infection until there are no new infections depends on driving the number of secondary infections produced by a typical source infection in a completely susceptible population (basic reproduction number; R_0) down to less than 1. Components of R_0 that must be addressed are the number of sexual contacts the infectious person makes per unit of time (C), the probability of transmission per single sexual contact with the infectious person (P), and the duration that the infected person is infectious to others (D) ($R_0 = C \times P \times D$). Numerous strategies may contribute to driving transmission of HIV infection down to zero, including early initiation of antiretroviral treatment and pre- or postexposure prophylaxis. This article summarizes a presentation by Davey M. Smith, MD, at the IAS–USA continuing education program held in San Francisco, California, in March 2015.

Keywords: HIV, transmission, transmission probability, infectiousness, duration of infectiousness, susceptible populations, basic reproduction number, reproductive rate, getting to zero

On World AIDS Day in 2012, the goal of "getting to zero" new cases of HIV infection was articulated.[1] More than 2 years later, there are approximately 1.2 million people in the United States living with HIV, and approximately 1 in 5 are unaware of their infection. The incidence of HIV infection has remained stable for the past decade at an estimated 50,000 new infections each year. After 30 years of research, there is still no globally effective vaccine or cure for HIV infection.

Basic Reproduction Number

The goal of driving a communicable disease down to no new cases can be evaluated by determining what proportion of susceptible (ie, uninfected) people in a population must be protected (eg, by vaccination, preexposure prophylaxis [PrEP], etc) in relation to the particular reproductive rate of the infectious disease. In standard epidemiology, this is often characterized as the basic reproduction number (R_0). The R_0 is calculated by the number of sexual contacts an infectious person makes per unit of time (C) multiplied by the probability of transmission per single sexual contact with an infectious person (P) and the duration that an infected person is infectious to others (D); ($R_0 = C \times P \times D$).

The R_0 is the number of secondary infections produced by a typical source infection in a completely susceptible population. If a certain infectious agent has an R_0 of 4, for example, then an infected individual is expected to pass the infection to 4 individuals and each of those 4 would then pass the infection to 4 more individuals. If a preventive measure, such as a vaccine or PrEP, is used to protect 3 of 4 susceptible people at each step of this progression, then each infected person would pass the infection to only 1 susceptible person at each step. If the R_0 of an infection can be reduced to less than 1, the epidemic eventually dies out (ie, there are no new transmissions). For an infection with an R_0 of 4, 75% of the susceptible population must be rendered unsusceptible. Figure 1 shows R_0 values for communicable diseases and the estimated herd immunity threshold (proportion protected from transmission) needed to halt transmission.[2]

The R_0 for HIV infection varies among susceptible populations. For example, it would differ greatly between gay men and heterosexual men in San Diego, California, or between heterosexual individuals in Uganda and injection drug users in Southeast Asia. However, it is estimated that the R_0 of HIV infection is between 2 and 5 and that the herd immunity threshold needed to achieve an R_0 of less than 1 ranges from 40% to 80%.

Number of Sexual Contacts

Each component of R_0 is subject to considerable variation. For C (number of sexual contacts the infectious person has per unit of time), factors such as "sexual budget" (how many times a person has sex in a given period of time) or frequency of needle sharing for injection drug use should be taken into account. With regard to sexual transmission of HIV infection, monogamy, serial monogamy, and concurrency (one person having sex with various partners over a given

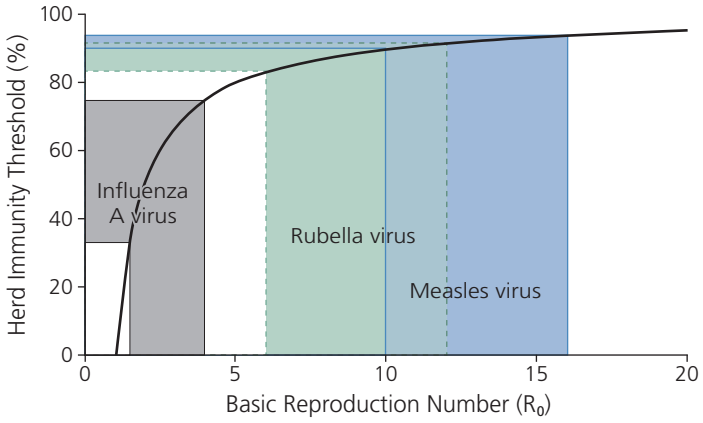

Figure 1. R_0 and herd immunity thresholds for select communicable diseases. In standard epidemiology, R_0 is equal to the number of sexual contacts the infectious person makes per unit of time (C) multiplied by the probability of transmission per single sexual contact with the infectious person (P) and the duration that the infected person is infectious to others (D) ($R_0 = C \times P \times D$). Adapted from Fine et al.[2]

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time period or set of sexual encounters) yield different infection rates. In particular, if 1 in 8 persons is HIV infected and is serially monogamous, then 1 new infection would be expected after 1 round of sexual partnership and 3 new infections would be expected after 2 rounds. If 1 in 8 HIV-infected persons was concurrently having sex with a main partner and regularly with 2 additional partners, 3 new infections would be expected after 1 round of sexual partnerships and 6 new infections would be excepted after 2 rounds.

Probability of Transmission

Many factors influence the P (probability of transmission per sexual contact with the infectious person) of HIV infection, including biologic factors such as stage of infection, viral load in blood and genital secretions, presence of other sexually transmitted infections (STIs), circumcision, host genetics, and use of antiretroviral agents (eg, PrEP, postexposure prophylaxis [PEP], and microbicides), as well as behavioral factors such as sexual contact and positioning, serosorting, condom use, and substance use (eg, methamphetamines).

With regard to stage of HIV infection, the rate of infection per number of sexual contacts is highest during early infection and during very late infection, reflecting higher blood viral loads during these periods.[3,4] In association with such factors as immune activation and increased viral load in genital secretions, STIs (eg, chlamydia, syphilis, gonorrhea, trichomoniasis, and herpes simplex virus) markedly increase the risk of HIV transmission, especially in Africa. Circumcision has been shown to reduce the risk of HIV transmission to uninfected men but not to female partners of HIV-seropositive men.

Use of vaginal tenofovir microbicide gel reduced HIV transmission in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial among heterosexual African women, although the "messiness" of the gel affected adherence.[5] PrEP with tenofovir and emtricitabine in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study was associated with a significant ($P = .005$) reduction in HIV transmission.[6] However, questions remain about when microbicides and PrEP should be used, appropriate dosage, how they will be paid for, and how many people in a population should receive them.

With regard to protective vaccines, one study showed the protective effect ($P = .04$) of a candidate vaccine given to more than 16,000 heterosexual men and women.[7] However, the borderline significance of the protective effect and the absence of knowledge of correlates of protection require further study.

Duration of Infectiousness

With regard to D (duration that the infected person is infectious to others), a primary factor to consider is that potent antiretroviral therapy allows HIV-infected individuals to live longer, increasing the number of individuals living with HIV. Limiting the duration of infectiousness in a growing population of HIV-infected individuals who are living longer should be a primary focus.

Testing for acute HIV infection may impact the duration of infectiousness. In San Diego, the institution of a program for testing for acute HIV infection in a region with the highest incidence and prevalence of HIV infection among 5 regions in the same county was associated with a marked reduction in HIV incidence versus expected incidence in that region, whereas incidence in the other regions remained relatively constant.[8] Analysis suggested that this was not attributable to differences in the prevalence of other STIs or to viral suppression rates during treatment in HIV clinics. It is thought that testing for acute HIV infection linked infected individuals to care sooner, limiting the period of high infectiousness during early infection.

There is considerable evidence that antiretroviral treatment and earlier initiation of treatment reduce infectiousness. Cohen and colleagues showed that initiation of antiretroviral treatment in HIV-infected persons at time of diagnosis reduced the risk of transmission to uninfected partners compared with waiting to start treatment until CD4+ cell count was below 350/μL.[9] A meta-analysis in 2009 reported a transmission rate of near 0 per 100 person-years among HIV-infected individuals taking antiretroviral therapy who had plasma HIV RNA levels below 400 copies/mL. The transmission rate increased from 2.06 per 100 person-years to 9.03 per 100 person-years among HIV-infected individuals not on antiretroviral treatment whose HIV RNA levels increased from in the range of 400 copies/mL to 3499 copies/mL to greater than or equal to 50,000 copies/mL.[10]

Figure 2 shows a model developed by Granich and colleagues that estimates the incidence of HIV infection over time with no antiretroviral treatment, antiretroviral treatment initiated at CD4+ cell counts of less than 350/μL, or universal voluntary HIV testing with antiretroviral treatment initiated at time of diagnosis of HIV infection.[11] Universal HIV testing and immediate treatment are estimated to ultimately produce an incidence rate approaching 0.

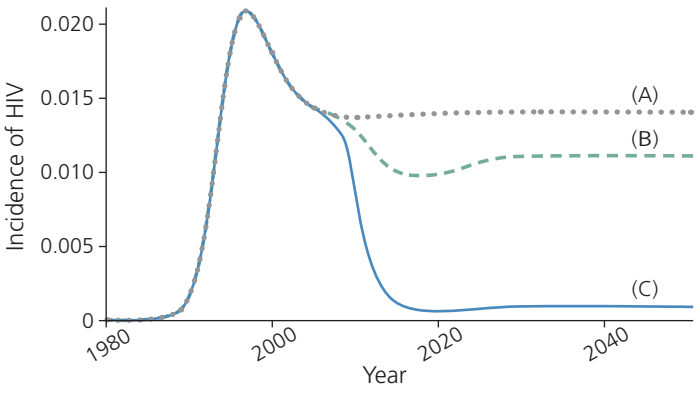

Figure 2. Changes in HIV incidence with no antiretroviral treatment (A), antiretroviral treatment initiated at CD4+ cell counts of less than 350/μL (B), or universal voluntary HIV testing with antiretroviral treatment initiated at time of diagnosis of HIV infection (C). Adapted from Granich et al.[11]

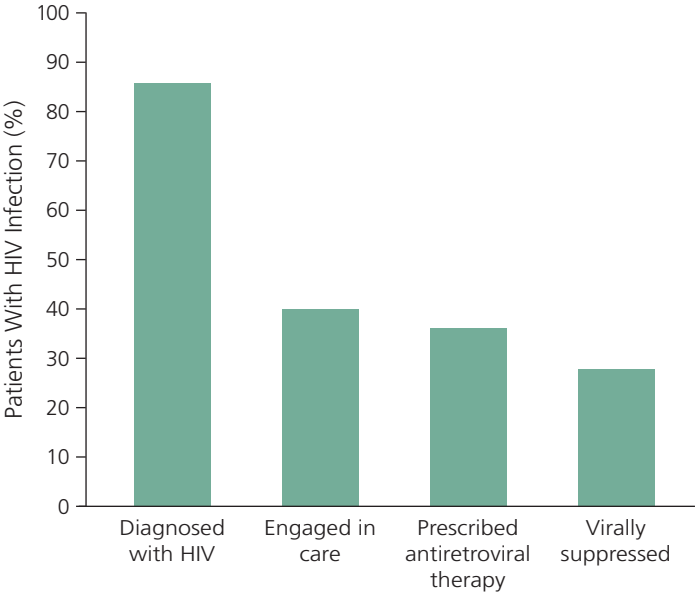

Figure 3. The Gardner Cascade, showing where improvements are needed in the HIV care continuum in order to substantially reduce HIV transmission and the duration of infectiousness. Adapted from Gardner et al.[12]

The Gardner Cascade, based on a report by Gardner and colleagues in 2011, shows where improvements are needed in the HIV care continuum in order to substantially reduce HIV transmission and the duration of infectiousness (Figure 3).[12] Of the approximately 1.2 million people estimated to be living with HIV infection in the United States, approximately 86% are diagnosed, 40% are engaged in care, 37% have been prescribed antiretroviral therapy, and 30% are virally suppressed. Thus, duration of infectiousness is prolonged in approximately 70% of HIV-infected individuals.

Future Directions

A plan to drive R_0 down to less than 1 in the United Kingdom involves promoting condom use, behavioral changes, and use of PrEP and PEP, microbicides, or antiretroviral treatment. A similar plan in San Francisco, California, involves promoting the use of PrEP, rapid HIV testing and treatment, and retention in care. Successful strategies are likely to depend on HIV testing and treatment; retention in care; testing and treatment for other STIs; use of PrEP, PEP, or microbicides; condom use; clean needle programs; circumcision; and likely other measures that have yet to be defined.

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