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Topics in Antiviral Medicine™

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Perspective CME

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Topics in Antiviral Medicine™

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- Describe the diagnosis and treatment of latent tuberculosis infection
- Identify strategies and interventions to improve linkage to and engagement with HIV care
- Outline the major potential health effects of the warming earth on the HIV-1–infected population

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Perspective

New and Noteworthy in Tuberculosis Diagnostics and Treatment

People with HIV infection with latent tuberculosis (TB) infection (LTBI) are at a 10-fold greater risk of developing active disease. Interferon gamma release assays and tuberculin skin testing have approximately 65% to 70% specificity for diagnosing LTBI in HIV-infected patients. LTBI can be successfully treated with isoniazid preventive therapy and early antiretroviral therapy (ART). Rapid molecular diagnostics have approximately 88% sensitivity and 98% specificity for identifying active TB. ART should be started early in patients with TB. A number of ART regimens are recommended in co-treatment that minimize the risk of drug-drug interactions. Although progress has been made, better diagnostics and TB regimens with lower risks of drug-drug interactions and shorter treatment durations are still needed. This article summarizes a presentation by Susan Swindells, MBBS, at the Ryan White HIV/AIDS Program Clinical Care Conference held in San Antonio in August 2017.

Keywords: HIV, TB, diagnosis, treatment, drug-drug interactions

Tuberculosis (TB) remains a major global health problem (Figure 1).[1,2] It is estimated that 23% of the world's population is infected with TB. World Health Organization (WHO) data for 2016 indicate approximately 10 million new cases of active TB disease, with 10% occurring in individuals with HIV infection, and 1.7 million deaths (>1000 deaths per day), with 400,000 occurring in HIV-infected persons.

Latent Tuberculosis Infection Testing

Consider the case of a 34-year-old man who emigrated from Mexico to the United States 6 years ago and is establishing care. He was diagnosed with HIV infection 6 months ago when he was hospitalized with community acquired pneumonia and was started on tenofovir alafenamide (TAF), emtricitabine, elvitegravir, and cobicistat. His CD4+ cell count has increased to 120/µL and his plasma HIV-1 RNA level is undetectable. It is decided to test the patient for TB using an interferon gamma release assay (IGRA); the result comes back "indeterminate." Given the low CD4+ cell count, the best strategy in this case is to wait until there is additional increase in CD4+ count to above 200 cells/µL before repeating the test.

Risk of progression from latent tuberculosis infection (LTBI) to disease is 10-fold greater in persons with HIV infection than in persons with LTBI and no HIV infection. The Centers for Disease Control and Prevention (CDC) recommends testing for TB after HIV diagnosis and then annually if testing is negative or if there is exposure risk. If a patient has negative testing for TB infection before the initiation of antiretroviral therapy (ART), testing should be repeated after the initiation of ART. There is no direct diagnostic test for LTBI, but this is presumed from a positive tuberculin skin testing (TST) or IGRA. Neither test predicts risk of progression to active TB. There is no benefit to repeating either test once a positive result is obtained. LTBI testing should not be used to diagnose active TB.

TST and IGRA each have approximately 65% to 70% sensitivity for diagnosing LTBI in patients with HIV infection. The TST requires 2 visits, has the same interpretation regardless of whether the patient has had Bacillus Calmette-Guérin (BCG) vaccine, and the actual test is less expensive than IGRA. It also requires training to administer and interpret. IGRA testing requires a single visit, is also unaffected by prior BCG vaccination, and requires that the blood sample be processed within 8 to 30 hours. Results can be positive, negative, or indeterminate, with an indeterminate result being more common with immunosuppression (eg, CD4+ cell count <200/µL). Restoration of CD4 cell number and function with ART improves performance of the test. There are limited data on its use in young children or those with recent exposure.

Treatment of LTBI

With regard to the patient case, after 6 months of ART, his CD4+ cell count is 300/µL. The repeat IGRA is positive; the patient has no signs or symptoms of active TB and has a normal chest x-ray. How should the patient be treated for LTBI?

The CDC recommendations for treatment of LTBI in HIV consist of isoniazid (INH) daily or twice weekly for 9 months, INH plus rifapentine weekly for 12 weeks, or rifampin (or

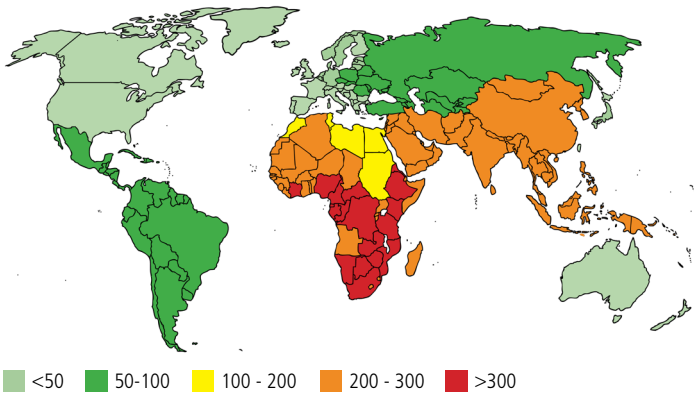

Figure 1. Cases of tuberculosis per 100,000 people.[1,20]

Dr Swindells is Professor of Internal Medicine and the Medical Director of the HIV Clinic at the University of Nebraska Medical Center.

rifabutin) daily for 4 months. A recent study of 1 month of daily INH with rifapentine in 3000 people with HIV infection was noninferior to 9 months of INH, had fewer adverse events, and was more likely to be completed. This ultrashort course TB preventive therapy could be an important new tool to control HIV-related TB.[3] Patients should be monitored monthly for hepatitis and other adverse effects.

Since rifamycins are potent inducers of metabolizing enzymes, the 2 rifamycin-based regimens pose problems with potential drug-drug interactions in patients on ART and other medications. General guidelines are that any ART regimen can be used when INH alone is used for LTBI treatment. However, only efavirenz (EFV) or raltegravir based regimens can be used with once-weekly INH plus rifapentine, and TAF is contraindicated. The potential for drug-drug interactions with rifamycins needs to be carefully assessed. EFV or double-dose dolutegravir can be used with rifampin. A protease inhibitor (PI) can be used with rifabutin at 150 mg daily or 300 mg 3 times a week. Further detailed information can be found at the following sites:

- https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
- http://www.hiv-druginteractions.org.

Treatment for LTBI in patients with HIV infection is effective. A 2006 meta-analysis of 11 randomized trials including 8130 participants with HIV infection showed that INH preventive therapy (IPT) was associated with a 36% reduction in risk for active disease, with a 62% reduction observed among those with a positive TST.[4] Other data indicate a preventive benefit with early initiation of ART. In the Temprano trial in Côte d'Ivoire, 2056 patients with CD4+ cell counts below 800/µL were randomly assigned to immediate or deferred ART with or without IPT.[5] The 30-month probability of death or severe HIV-related illness was 14.1% in the deferred ART group, 8.8% in the deferred ART plus IPT group, 7.4% in the early ART group, and 5.7% in the early ART plus IPT group. TB accounted for 43% of the end points. Early ART and IPT were independently associated with reduced risk of TB.

Diagnosis of Active TB

In a second patient case, a 54-year-old woman is admitted to the hospital with cough, fever, and weight loss. She is diagnosed with HIV infection on admission, with a CD4+ count of 70 cells/µL and plasma HIV-1 RNA count of 120,000 copies/mL. Chest x-ray shows pleural thickening and diffuse infiltrate; sputum acid-fast bacillus testing is negative, as is bronchoscopy for *Pneumocystis jirovecii*.

Light microscopy was the staple of TB diagnostics for 2 centuries, and still is in many parts of the world. We now have rapid molecular diagnostics that perform better and are much simpler. The first to become available was the Xpert MTB/RIF assay. With this assay, patient sputum is put into a small cartridge, inserted into the machine, and 'yes/no' results are available in 2 hours for TB, and if positive, for rifampin resistance. The assay is more sensitive than smear testing, works in children and extrapulmonary TB, and permits screening for drug-resistant TB.[6]

A recent study by the AIDS Clinical Trials Group on 992 participants from numerous US sites and sites in South Africa and Brazil, including 45% with HIV infection (median CD4+ cell count, 151/µL), assessed the Xpert MTB/RIF assay for identifying pulmonary TB.[7] The overall sensitivity of the assay in US participants was 85.2%, including sensitivity of 96.7% in smear-positive/culture-positive cases and 59.3% in smear-negative/culture-positive cases. Overall specificity for 2 tests was 98.9%, including 100% in smear-positive/culture-positive cases and 98.9% in smear-negative/culture-positive cases. It is noteworthy that the very high specificity of the assay provides enough confidence in negative results that hospitalized patients with negative results can be removed from respiratory isolation.

ART and TB Treatment

The patient in the current case is diagnosed with TB on the Xpert MTB/RIF assay, with culture results pending. She is started on treatment with the standard 4-drug regimen of INH, rifampin, ethambutol, and pyrazinamide. When should ART be started?

ART should be started early. The rationale is based on findings of the large-scale CAMELIA (Cambodia),[8] SAPIT (South Africa),[9] and STRIDE (international) trials,[10] which examined immediate TB therapy with ART started at 2 weeks or started at 8 weeks. The CAMELIA trial showed a 34% reduction in all-cause mortality ($P = .004$) for immediate vs delayed ART; the STRIDE study showed a 19% reduction in risk for AIDS or death with immediate vs delayed ART ($P = .45$); and the SAPIT trial showed an 11% reduction in risk for AIDS or death with immediate vs delayed ART ($P = .73$). The benefit of earlier ART was most pronounced in patients with lower CD4+ cell counts. Earlier ART was also associated with some increase in risk for immune reconstitution inflammatory syndrome (IRIS).

Currently, WHO,[11] American Thoracic Society,[12] IAS-USA,[13] and US Department of Health and Human Services[14] guidelines all recommend initiation of ART within 2 weeks for those with CD4+ cell counts less than 50/µL and within 8 weeks for those with CD4+ cell counts greater than 50/µL. An exception is when TB meningitis is present, given the findings in a randomized trial showing increased adverse events and deaths with early ART.[15]

HIV/TB co-treatment options for adults are shown in Table 1. The most clinical experience is with EFV plus 2 nucleoside reverse transcriptase inhibitors (RTIs) if rifampin is being used and a ritonavir–boosted PI plus 2 RTIs if rifabutin is being used. Alternative regimens consist of raltegravir or dolutegravir plus 2 RTIs with rifampin.

Currently, TAF use is contraindicated with rifamycins. Tenofovir disoproxil fumarate (TDF) has been studied with rifampin without substantial drug-drug interactions being observed. However, based on modeling data, carbamazepine reduced TAF exposure by 55% and TAF is known to be more

Table 1. Recommendations for drug dose adjustments for HIV/tuberculosis cotreatment

ARV[a]	Rifamycin	Dose Adjustment	Comments	
Efavirenz	Rifampin	None		
Lopinavir/ritonavir or Darunavir/ritonavir	Rifabutin	Rifabutin 150 mg once daily	Monitor for uveitis	
Raltegravir	Rifampin	Raltegravir 800 mg twice daily	Limited clinical experience	Do not administer raltegravir 1200 mg once daily with rifampin
Dolutegravir	Rifampin	Dolutegravir 50 mg twice daily	Limited clinical experience	

[a]All ARV to be given with 2 reverse transciptase inhibitors but not with tenofovir alafenamide.

highly affected by P-glycoprotein induction than TDF. Interaction studies of TAF with rifamycins in humans are ongoing.

Rifabutin is often used for TB treatment in the US, because the drug has fewer interactions and can be used with boosted PIs in individuals with HIV infection. However, a Cochrane review found that there are "insufficient data to be assured of the effectiveness of rifabutin in TB treatment".[16] Furthermore, clinical trials comparing rifabutin with rifampin largely have been conducted among patients not on ART. In addition, the correct dose is uncertain; most pharmacokinetics studies have been done in uninfected volunteers, and there are data to suggest that 300 mg 3 times a week is insufficient in patients with HIV infection. The agent poses risk of uveitis, is expensive, and has no pediatric formulation.

With regard to ART, the prescribing information for single-agent EFV, but not co-formulated products including EFV, states that if the drug is co-administered with rifampin to patients weighing 50 kg or more, an increase in the dose of EFV to 800 mg once daily is recommended. In the author's opinion, this recommendation is wrong, having been based on studies in non-infected volunteers. Co-administration in patients who have HIV and TB paradoxically results in increased rather than decreased EFV exposure.[17] Thus, in co-treatment, the EFV dose does not need to be increased.

With regard to the patient case, she starts ART at 2 weeks, and 10 days later has recurrent fever, followed by worsening dyspnea and cough. A chest x-ray shows progression of pulmonary infiltrates. IRIS is suspected.

IRIS is more common with early ART in those with low CD4+ cell counts. It is rarely severe or fatal, and the possibility of its occurrence should not delay start of ART. Management includes making certain of the diagnosis, ruling out drug-resistant TB or a new opportunistic infection, and then surgical drainage, use of nonsteroidal antiinflammatory drugs (although the quality of evidence of benefit is low), and use of prednisone. A prednisone regimen of 1.5 mg/kg per day for 2 weeks and then 0.75 mg/kg per day for 2 weeks reduced the risk of adverse events in a randomized trial in hospitalized patients.[18] However, more data to support this approach are lacking. A study evaluating prophylactic prednisone (40 mg/day for 2 weeks followed by 20 mg/day for 2 weeks) has shown some promise in high risk patients.[19]

Conclusion

TB disease can be prevented by treating HIV and by treating LTBI. There have been major improvements in TB diagnostics, however, there are not enough new drugs in the pipeline. New options include bedaquiline, which is approved for use in the US, and delamanid, which will soon be approved; each is active against drug-resistant TB. Although drug-drug interactions complicate HIV and TB co-treatment, TB and HIV should be treated concurrently, and safe and effective regimens are available. More research investment and advocacy are needed to help us reach the goals of better TB regimens with lower risk of drug-drug interactions and shorter treatment durations, and better treatments for infected children.

Presented by Dr Swindells in August 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Swindells in May 2018.

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Perspective

Strategies for Linkage to and Engagement With Care: Focus on Intervention

Retention of HIV-infected patients in care is crucial to optimizing individual patient outcomes and reducing transmission of HIV. A number of strategies are available to improve linkage to care; among them, the Anti-Retroviral Treatment and Access Services intervention should be considered standard of care at the clinic level. With regard to retention in care, the Retention Through Enhanced Personal Contact intervention has been shown to improve retention rates and the Centers for Disease Control and Prevention Data to Care program has been successful in assisting public health authorities to locate and return to treatment patients presumed to be lost to follow-up. Patient satisfaction with initial physician and clinic encounters also improves retention. There are some data to support same-day or rapid start of antiretroviral therapy in the clinic setting as a method to immediately establish care and more data on this approach are needed. This article summarizes a presentation by Thomas P. Giordano, MD, MPH, at the Ryan White HIV/AIDS Program Clinical Conference held in San Antonio, Texas, in August 2017.

Keywords: HIV care, engagement, linkage, retention, cascade, ARTAS, REPC, Data to Care, same-day ART

The HIV care process is best viewed as a continuum running from 'not engaged in care' to 'fully engaged in care' (Figure 1).[1] HIV-infected patients can and do move back and forth along the continuum. The goal for clinicians is to keep patients as fully engaged as possible so that their clinical outcomes are optimized, which requires ongoing efforts. In essence, as many HIV-infected people as possible should get into care, be retained there, start, and remain on antiretroviral therapy (ART) with undetectable plasma HIV-RNA. This needs to be done for the health of individual patients, and because of the public health benefit of having patients fully engaged in care and fully virologically suppressed, and thus less likely to transmit infection. The Centers for Disease Control and Prevention (CDC) estimates that whereas approximately 30% of cases of HIV transmission are from persons who are unaware that they are infected, more than half are from persons who are aware of their HIV infection but not retained in care.

Linkage to Care

Linkage to care is defined as a completed visit with a practitioner who can prescribe ART. The goal is to establish linkage within 30 days of diagnosis. Linkage should be monitored by the diagnosing site and by the clinical site once a patient "touches" the clinical site. Linkage to care efforts must be delivered with sensitivity and persistence.

Numerous factors affect linkage to care. Among patient factors, younger age, African American race, and injection drug use are associated with delayed linkage to care, as are other active substance use, mental health problems, and stigma. Greater disease severity is associated with higher likelihood of linkage. More limited socioeconomic resources, opportunity costs (eg, missing work days to obtain care), and unmet needs (eg, food, housing, money, transportation) are all barriers to linkage. Health system factors that can improve linkage include colocation of testing and treatment services, and minimizing the time gap between diagnosis and clinic intake. Active linkage services (eg, assisting the patient in setting up appointments, maintaining an active relationship with the patient until linked, and providing linkage case management) also greatly increase the likelihood of successful linkage compared with passive linkage (eg, only providing names and contact information for treatment centers). Copays and problems with insurance are barriers to linkage. More rapid access to treatment and ART after seeking care improves linkage. For example, linkage rates are higher when patients seeking care are given physician appointments within 1 or 2 weeks rather than 6 weeks.

The only randomized clinical trial that has examined an intervention to improve linkage to care is the ARTAS (Anti-Retroviral Treatment and Access to Services) trial, reported in 2005 and led by Gardner and colleagues from the CDC.[2,3] The study involved 273 participants in 4 cities, with 78% diagnosed with HIV infection within the prior 6 months. Patients were randomly assigned to receive 90 days or 5 sessions of strength-based case management or to passive linkage (standard of care). The strength-based management was delivered by what would now be called patient navigators (not licensed practitioners), who were trained in the intervention. The navigators met the patients in the patients' environment and helped them identify what life strengths they had and then guided the patients in formulating goals for their HIV treatment. The navigators used elements of motivational interviewing in working with the patients. Linkage rates for the intervention vs standard care groups were 78% and 60%, respectively, at 6 months and 64% and 49%, respectively, at 12 months. Based on this success, the CDC has formulated the ARTAS intervention for dissemination and training purposes and the program has been instituted in non-academic community settings, including public health departments that train their disease intervention specialists in the intervention. The ARTAS linkage strategy should be the standard of care for HIV testing programs as well as for clinic staff who work with patients in linking to care.

Dr Giordano is Associate Professor of Medicine at Baylor College of Medicine in Houston, Texas.

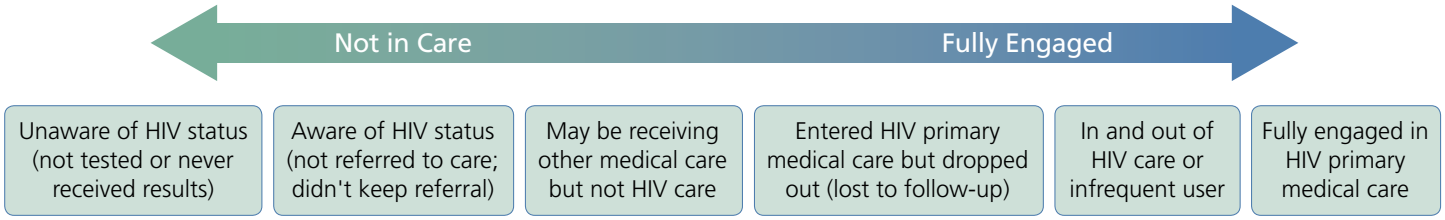

Figure 1. Health Resources and Services Administration HIV continuum of care. Adapted from Cheever, *CID*, 2007.[1]

Retention in Care

Retention in care is defined by various measures, including constancy measures (eg, at least 2 visits in a year at least 90 days apart), visit adherence measures (eg, number or proportion of visits that are missed), or both. Each has been independently associated with survival. In addition, a simple clinically applicable measure is to ask "how long has it been since you saw this patient?", because the duration of gap in attendance provides a useful idea of whether the patient is adhering to treatment. Retention should be monitored, especially for newer patients and patients with detectable HIV viral load. Retention efforts must be delivered with sensitivity and persistence.

Patient and health system factors affecting retention in care include all those affecting linkage. Recent incarceration is an additional patient factor shown to impede retention. Poorer patient-practitioner relationships and lower trust in practitioners are health system factors that impede retention. Flexible appointment schedules, expanded clinic hours, and copay, financial, or insurance assistance (eg, via the Ryan White HIV/AIDS program) improve the likelihood of uninterrupted access to and retention in care.

Only 1 randomized clinical trial has shown benefit of an intervention designed to improve retention in care in the general US clinical setting. The Retention Through Enhanced Personal Contact (REPC) intervention was assessed by Gardner et al in 6 US HIV clinics.[4] Patients were randomly assigned to 1 of 3 arms consisting of usual care (n = 613), moderate intensity intervention (enhanced contact; n = 615), and higher intensity intervention (enhanced contact with skills; n = 610). Eligible patients were those appearing at a clinic visit who had past poor retention in care. Outcomes with the moderate intensity intervention were equivalent to those with the higher intensity intervention. The moderate intensity intervention included a 20-minute HIV education session with a "retention specialist" (an unlicensed patient navigator) and scheduling of a visit with the patient's primary care physician. The patient received a telephone call from the retention specialist midway between the recruiting clinic visit and the next scheduled appointment checking on his or her status, reminding the patient of the upcoming visit, and querying whether the patient needed assistance in attending the visit. Telephone contact was repeated at 7 days and 2 days before the visit. At the visit, the retention specialist greeted the patient in person, asked about the patient's status, and offered to assist in linking to other available services (eg, substance use services and transportation assistance) available in the clinic outside the study. Patients missing the visit were immediately contacted by phone to reschedule, assess barriers to attendance, and offer linkage to services to overcome the barriers. The enhanced support was provided around all scheduled HIV primary care visits for 1 year. At the author's clinic, 2 retention coordinators worked with more than 200 patients in this way.

During the 2010 to 2012 study period, visit constancy (% of patients with a visit in each of 3 consecutive 4-month intervals) was 45.7% in the usual care group and 55.8% in the moderate intensity group (risk ratio [RR], 1.22; 95% confidence interval [CI], 1.09-1.36), and 55.8% in the higher intensity group (RR, 1.22; 95% CI, 1.09-1.36). Visit adherence (kept visits divided by scheduled appointments, excluding canceled appointments) was 67.2% in the usual care group and 72.5% in the moderate intensity group (RR, 1.08; 95% CI, 1.05-1.11), and 70.9% in the higher intensity group (RR, 1.06; 95% CI, 1.02-1.09). The intervention improved retention in most subgroups examined, including among patients with detectable viral load, those with low CD4+ cell count, younger patients, patients in a racial or ethnic minority group, and those with public or no insurance. Efficacy was not observed among active substance users or patients with a severe unmet need such as food or housing. The CDC is currently formulating the REPC intervention for dissemination and training, as it did with the ARTAS intervention.

Other measures that have been reported to improve retention in care include in-clinic opioid replacement therapy for opioid users and use of electronic medical records to alert practitioners when patients have suboptimal follow-up or high viral load. Data from non-randomized studies support such measures as clinic-wide marketing (eg, posters, brochures, and customer service training) to promote attendance and provide patients a welcoming and courteous experience, stepped case management, social work, and outreach services. There have been mixed data on use of patient navigators, supporters, and peers, and provision of financial incentives. A 12-session peer navigation intervention that started pre-release did achieve higher rates of HIV suppression than in the control group 1 year after persons were released from jail in Los Angeles.[5]

The CDC Data to Care program is designed to assist public health authorities in identifying, locating, and reengaging patients who have been lost to care. Public health authorities such as city, county, or state health departments have access

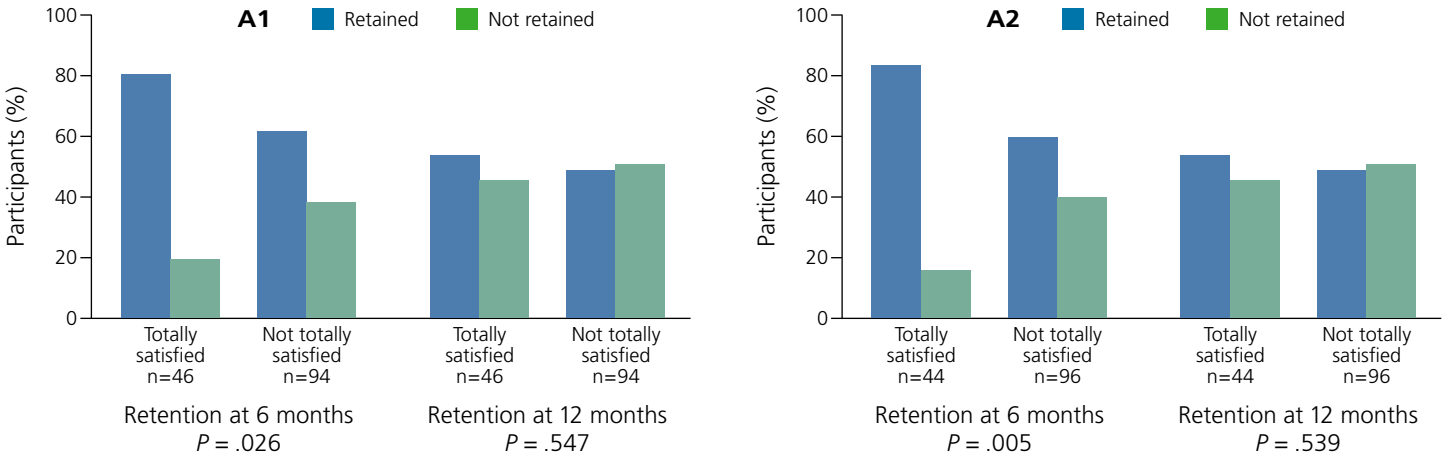

Figure 2. Retention in care according to patient satisfaction with initial HIV practitioner experience (A1) and initial HIV clinic experience (A2). Adapted from Dang, *AIDS Behav*, 2016.[7]

to information that may not be available to local clinics, including viral load and CD4+ cell count data from other clinics, current contact information, and information on whether a patient is alive or deceased, has moved to another geographic area, or has been incarcerated. In a study in New York City in 2008 to 2010, public health efforts to reengage HIV-infected patients located 684 (87%) of 797 patients presumed to be lost to follow-up in HIV care.[6] Of these, 409 (60%) were confirmed as lost to follow-up; among those lost to follow-up, 315 (77%) were relinked to care and 94 (23%) refused linkage. Of the 315 linked to care, 240 (76%) returned to care. Results of such public health efforts in other locales have been mixed.

A more recent study has shown that patients' satisfaction with their initial HIV practitioner encounter and initial HIV clinic encounter has a substantial effect on retention in care rates.[7] As shown in Figure 2, the difference in retention and non-retention rates between patients reporting total satisfaction or less than total satisfaction was statistically significant at 6 months for practitioner experience and for clinic experience. Greater retention rates were observed at 12 months, although the differences fell short of statistical significance. All clinic personnel should support retention by providing an optimal patient care experience, constructively affirming attendance rather than criticizing non-attendance, and collaboratively solving problems with patients to overcome barriers.

Rapid or Same-Day Treatment

Time from initial HIV diagnosis to starting ART can be weeks to months, with the typical process involving confirmatory testing, visit to the treatment site, determination of financial eligibility for care, pre-care (eg, laboratory testing for genotyping, viral load, CD4+ count, and other laboratory values, as well as counseling, etc), clinician visit including prescription of ART, and dispensing of ART.

Rapid or same-day treatment could eliminate the potential for patients being lost to care along this path by engaging them in care earlier. Patients may have better clinical outcomes resulting from less time off ART, and risk of HIV transmission from the patient is reduced if the patient is on suppressive ART. In addition, shorter time to treatment may result in less patient anxiety and more trust, because something is immediately being done to help the newly diagnosed patient. On the other hand, it is unlikely that a 2-month delay, for example, in starting ART will make a difference in clinical outcome; data on delayed therapy from the START (Strategic Timing of Antiretroviral Treatment), TEMPRANO, and HPTN (HIV Prevention Trials Network) trials suggest that such a delay is unlikely to substantially alter outcome. Starting ART immediately runs the risk of using antiretroviral drugs that laboratory work-up would show should not be used in a particular patient and also runs the risk of missing tuberculosis or another opportunistic infection that may require deferral of ART. Starting immediately also leaves less time to address barriers to ART and adherence. Being lost to follow-up prior to ART does not risk resistance, whereas emergence of resistance is an issue in patients lost to care after starting treatment. The strategy also adds logistical complexity (eg, paying for ART, appointment scheduling).

Evidence in favor of same-day or rapid ART has been provided by a small number of studies. The randomized RapIT trial South Africa[8] compressed pre-ART care into 1 visit and started ART on the same day. A randomized same-day ART study in Haiti[9] shifted the start of ART from the end of pre-ART care to the same day that the patient entered the clinic. The START-ART trial in Uganda,[10] which was randomized at the clinic level, reduced pre-ART care and started ART on same day as clinic entry. These studies provided consistent results, showing that starting ART immediately resulted in greater and faster HIV suppression, similar or better patient retention, and similar or better survival and that pre-ART care can be dramatically simplified. However, a high proportion of patients lost to follow-up had started ART. Further, the studies thus far have provided no data beyond 12 months, limited resistance data, and no patient-reported outcomes or mental health data.

Thus far, there appears to be only 1 published US study on rapid ART, the nonrandomized RAPID trial performed by Pilcher and colleagues at University of California San Francisco.[11] In the study, patients who had acute or recent HIV or very low CD4+ cell count were routed to rapid treatment (RAPID group), with other patients continuing in standard clinic care (non-RAPID group). Patients receiving rapid treatment could receive taxi vouchers for transportation to the clinic and had a first-day visit of 3 to 4 hours that included pre-ART care, rapid financial assistance, provision of a 5-day ART starter pack, and directly observed therapy of the first dose; nurse follow-up was performed within several days and a clinician visit occurred in 1 to 2 weeks. Overall, 90% of patients received an integrase strand transfer inhibitor (InSTI)-based regimen. Among 39 patients in the RAPID group and 47 in the non-RAPID group, ART was started on the day of the clinic visit in 35 vs 17; by 1 day in 37 vs 17; by day 7 in 38 vs 20; and by day 30 in 39 vs 32. There were 36 of 47 patients in the non-RAPID group who were on ART by day 90. The RAPID group had greater and more rapid viral suppression. Over limited follow-up, no safety or resistance issues were identified.

Summary

It is important to measure linkage and retention for clinic and practitioner populations and to expand efforts to find individuals in the gaps. There is no magic bullet for ensuring patient engagement in care, but a number of strategies will help to improve linkage and retention. Patient and clinic barriers to consistent care should be compassionately and constructively identified and addressed. Linkage can be improved by using the ARTAS linkage to care protocol, active linkage protocols, and good post-test counseling. Retention can be improved by using reminders and personal contact, addressing unmet needs, and minimizing clinic barriers, as well as by improving patient experience and patient satisfaction and building trust. Clinics should participate in data-to-care efforts and should attempt to minimize delays in treatment. More complete evaluations of rapid treatment strategies are needed.

Presented by Dr Giordano in August 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Giordano in May 2018.

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UPCOMING ACTIVITIES

Summer and Fall 2018

Interactive Webinars

Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for details. Upcoming webinars will cover the following topics:

Forgotten but Not Gone: Learning From the Hepatitis A Outbreak and Public Health Response in San Diego County—July 19, 2018
Presenter: Darcy A. Wooten, MD

Update From the 2018 International AIDS Conference—August 21, 2018
Presenter: Roy M. Gulick, MD, MPH

Treating HCV Infection: It Doesn't Get Much Better Than This—August 30, 2018
Presenter: Susanna Naggie, MD, MHS

Opioid Withdrawal, Opioid Substitution, and HIV Infection—September 11, 2018
Presenter: R. Douglas Bruce, MD

HIV and Cardiovascular Disease: A Tale of Two Epidemics—September 25, 2018
Presenter: Marshall J. Glesby, MD, PhD

Flexner's Fabulous Formulations: A Review of Long-Acting Antiretrovirals and Other New Investigational Drugs—October 11, 2018
Presenter: Charles W. Flexner, MD

Fall 2018

Intensive Small-Group Hepatitis Workshops

Save the date. *These CME workshops continue to feature cutting-edge, scientifically rigorous topics presented by leading experts in the field of hepatitis C virus (HCV) medicine. Visit the IAS–USA website for up-to-date information and webcasts of prior courses. This fall, IAS–USA live courses focusing on the management of HCV infection will be held in:*

Memphis, Tennessee—Friday, October 12, 2018

Alabam Area—Friday, October 19, 2018

Milwaukee, Wisconsin—Tuesday, November 6, 2018

Portland, Maine—Date TBD

New Orleans, Louisiana—Date TBD

Charleston, South Carolina—Date TBD

New York, New York—Date TBD

Year-Round

Cases on the Web

A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for a full list of Cases on the Web activities. Recent activities address the following topics:

Immunizations for HIV-Infected Adults
Authors: Brian T. Montague DO, MPH, MS; Steven C. Johnson MD, University of Colorado
Release date: Thursday, July 13, 2017.

Diagnosis and Management of Major or Persistent Depression in the HIV-Infected Patient
Authors: Jameela J. Francine Cournos MD, Columbia University; Milton L. Wainberg MD, Columbia College of Physicians and Surgeons.
Release date: Monday, February 16, 2015.

Ending the Epidemic in New York City: From Blueprint to Implementation
Author: Demetre C. Daskalakis MD, MPH, New York City Department of Health and Mental Hygiene.
Release date: Wednesday, September 28, 2016.

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Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for email updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities.

Perspective

Our Warming Planet: Is the HIV-1–Infected Population in the Crosshairs

Global climate change exacerbated by human energy use threatens to have a profound impact on human health, including from infectious diseases. Particularly vulnerable populations include the immunocompromised, including persons with HIV infection. Global warming can be expected to increase the geographic range of pathogens such as Vibrio cholerae *as well as vectors that transmit disease, including ticks and mosquitoes. Higher temperatures also contribute to increased pathogen and vector efficiency in spreading disease. Natural disasters due to climate change result in population displacement, increased population density, and living conditions conducive to the spread of infectious diseases. Political mobilization is crucial to implementing and enforcing policies for prudent energy use, reversing the drivers of global warming, and ensuring that we are prepared for the adverse health consequences of climate change. This article summarizes a presentation by Robert T. Schooley, MD, at the IAS-USA continuing education program held in Berkeley in May 2017.*

Keywords: Global warming, climate change, natural disasters, infectious diseases, disease vectors, cholera, dengue, HIV

Climate change is occurring. The world is warming. Within the scientific community there is clear consensus that this warming reflects not just planetary cycles of warming and cooling that have been present since the earth was formed, but changes caused by human actions. Human energy use is the primary driver climate change, and directly reflects the product of the number of humans on the planet and how much energy each person uses per day.

An urgent question that must be faced is: How do these changes affect humans from the perspectives of general effects and of health effects, including infectious disease–related morbidity and mortality? Direct effects of climate change include accelerated weather extremes resulting in increased air pollution and more heat waves, and a greater number of more-fragile humans who are more susceptible to infectious diseases. Indirect effects include changes in biophysical systems such as rising oceans and melting glaciers. Such changes can result in deterioration of social and economic structures and conditions, including loss of property, loss of jobs, large-scale population displacement, and poorer nutrition and reduced availability of food on a global scale. Among the vulnerable groups of persons in the setting of climate change and its consequences are those with immunodeficiency, including those with HIV infection.

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Infectious Disease and Climate Change

Climate change can influence risk of infectious diseases in variety of ways, including expansion of the ranges of pathogens and vectors (eg, ticks, mosquitoes), increases in pathogen or vector efficiency, and via the consequences of more frequent natural catastrophes (flood, drought, etc).

With regard to expansion of the range of pathogens, a prime example is the spread of *Vibrio cholerae*. *V. cholerae*, like many bacteria, grow better in warm water, high pH conditions, and where there is abundant chitin. Chitin is a product of plankton that flourish in the presence of nitrogen runoff into rivers. In rivers in India, for example, increased agriculture and fertilization of crops has resulted in increased levels of nitrogen in rivers, tidal estuaries, and ocean water, resulting in blooms of the blue green algae (phytoplankton) in which *V. cholerae* thrives.[1] Figure 1 shows the increase in surface temperature and increase in phytoplankton and *V. cholerae* populations over time in the North Atlantic Ocean, and the increasing number of cholera outbreaks as this has occurred.[2] Figure 1 also shows the alarming increase in seawater area capable of supporting *V. cholerae* that is projected to occur between 2016 and 2100.[3] Outbreaks of gastroenteritis due to *Vibrio parahaemolyticus* in Alaskan oysters from Prince William Sound have also recently been documented.[4] As shown in Figure 2, cases occurred as the daily water temperature in June 2004 rose to above 15°C. Figure 2 also shows the increase in mean water temperature that had occurred between 1976 and 2004.

An example of effects of changes in vector ranges is the northward spread of tick-borne encephalitis that has been observed as Sweden has warmed. The ticks (*Ixodes ricinus*) are dormant in winter and emerge when night temperatures rise above 4°C to 5°C. As shown in Figure 3, the number of cases of tick-borne encephalitis has increased with an increasing number of spring nights that have exceeded the temperature threshold of 5°C to 8°C.[5]

Dengue is another disease projected to undergo dramatic geographic spread with warming. Amplification of dengue virus in *Anopheles aegypti*, the mosquito vector, occurs at temperatures above 18°C. At higher temperatures, the virus grows faster in the mosquito and allows the mosquito to become infectious earlier in its life cycle.[6] Figure 4 shows reported outbreaks of dengue between 1970 and 1996, and projected areas at risk for dengue from 1990 to 2085.[7] A similar distribution might be expected for Zika, chikungunya, and yellow fever viruses, as well as *Plasmodium falciparum,* because these pathogens are spread by similar vectors.

Increased pathogen or vector efficiency comes along with warming, because higher temperatures are associated with increased pathogen and vector replication rates. Increased population density, whether due to the growth of the world's

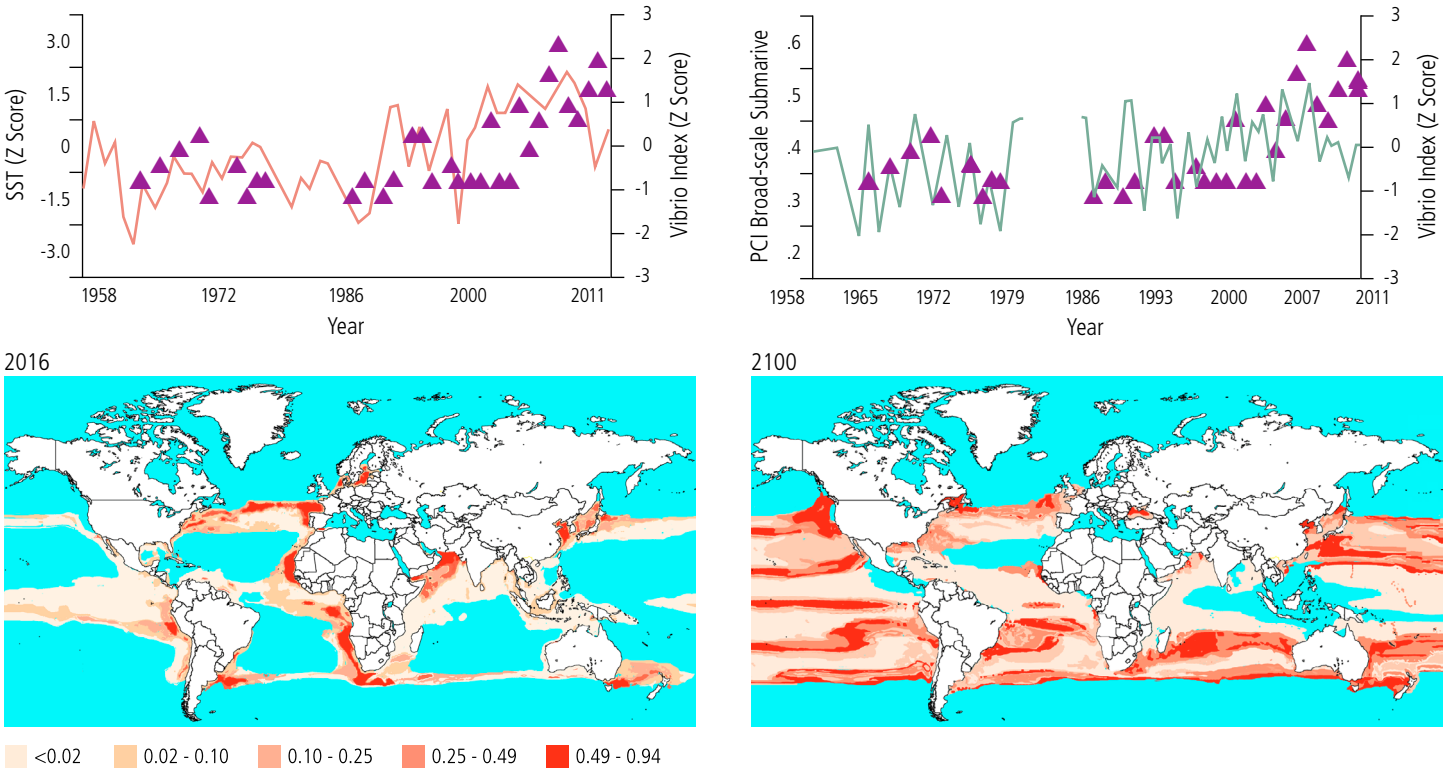


Figure 1. Top—Surface temperature and phytoplankton and Vibrio Index in the southern North Sea.[2] Bottom—seawater area capable of supporting *Vibrio cholerae* in 2016 and according to projection for 2100.[3]

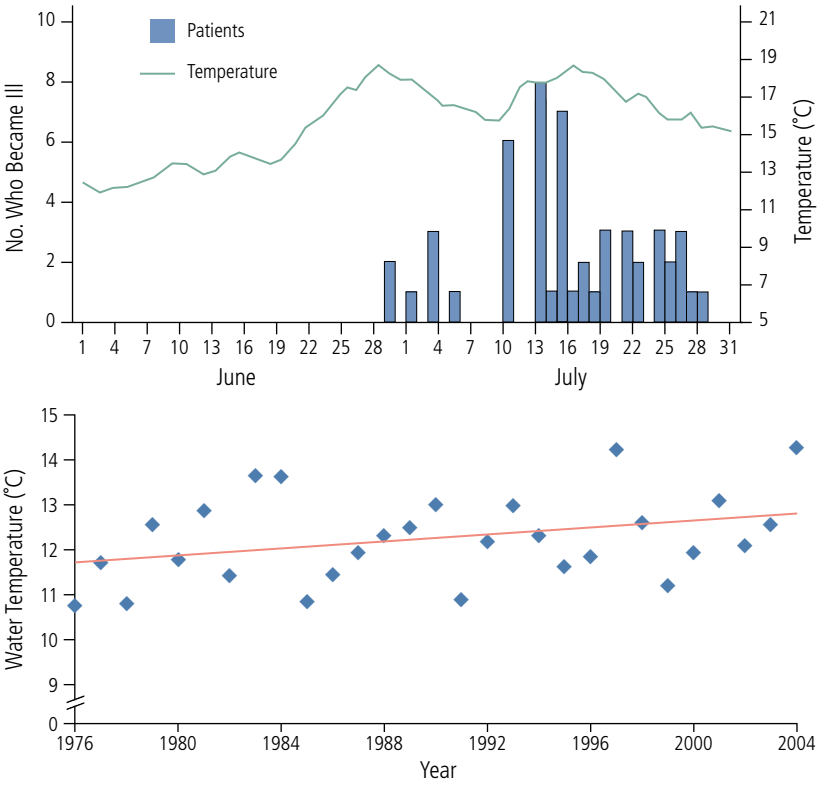
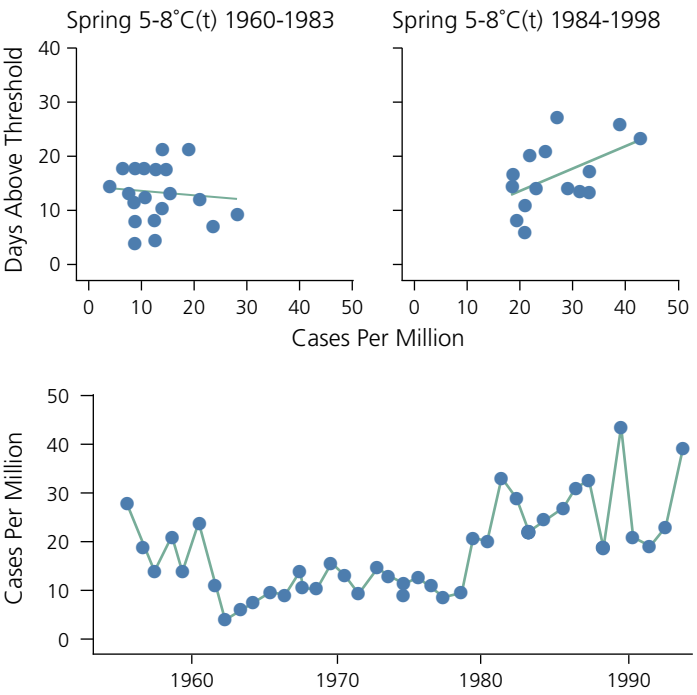


Figure 2. Top—Surface water temperature at a Prince William Sound oyster farm and number of cases of *Vibrio parahaemolyticus* infection. Bottom—Mean daily water temperature in the Gulf of Alaska, 1976-2004.[4]

population or to displacement caused by natural catastrophes related to climate change, or otherwise, allows the more efficient spread of many diseases, particularly respiratory and vector-borne diseases.

Natural catastrophes, including those associated with climate change, have a profound impact on spread of infectious diseases. Natural catastrophes do not affect all populations equally; there are greater negative effects on persons at the extremes of age, those in less affluent circumstances that may include insufficient housing, those with less food security (including the homeless), and those with already compromised health, including immunocompromised populations. These conditions also increase vulnerability to infectious diseases.

In many locales in Africa, sustained drought has affected agrarian society, with many people driven from rural area to cities, such as Cape Town and Nairobi. There, many live in impoverished, crowded conditions much more conducive to transmission of infectious diseases than habitation in farming areas. Floods in Haiti, Mozambique, and elsewhere have resulted in dislocation of populations to shanty towns, refugee camps, and other assemblages that have been stricken by cholera and dengue, and are more permissive of spread of tuberculosis and HIV.



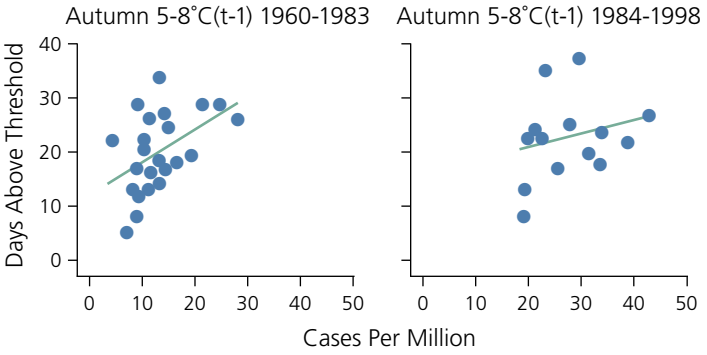


Figure 3. Relationship between spring and autumn temperatures and tick-borne encephalitis (TBE) in Sweden.[5]

The following select list shows some of the infectious disease consequences of recent natural disasters:

- Flooding
  - Cholera and enterotoxigenic *Escherichia coli*: Bangladesh 1998 and 2004
  - *Salmonella enterica*, *Cryptosporidium parvum*, and hepatitis A and E: Indonesia 1992, 2002, and 2004
  - Norovirus, salmonella, *V cholerae*: Hurricane Katrina in US 2003
  - Leptospirosis: Taiwan 2001, Brazil 1996, and Puerto Rico 2017 and 2018
- Crowding
  - Measles: Philippines after the Pinatubo eruption and Pakistan after the 2005 earthquake
  - Meningitis: Pakistan after the 2005 earthquake
  - Vector-borne diseases: Malaria in numerous locations after flooding and earthquakes
- Others
  - Tetanus and mucormycosis: following natural disasters and associated trauma in numerous locations
  - Coccidiodomycosis: California following dust storms triggered by earthquake-driven landslides

Outbreaks of disease in the setting of climate change are multifactorial, as illustrated by the Zika virus outbreak in Brazil. The El Niño drove a drying and warming condition in northeastern Brazil, where Zika first appeared. Mosquitoes can flourish in these conditions, with the drying of rivers leaving standing pools of water in which mosquitos can more readily replicate. With the drying of the rivers, people began to bring water to their homes in buckets, also a perfect breeding ground for the vector mosquitoes. The public health awareness of outbreaks was low, as Zika virus disproportionately affected people in lower economic conditions. Pregnant women and immunocompromised persons were further disproportionately affected by the disease.

Combating Infectious Morbidity From Climate Change—What Can We Do?

What can we do about the climate changes caused by human energy use, and infectious morbidity related to these changes? Climate-independent interventions include epidemic surveillance and mobilization capacity at local and multinational levels; maintaining vaccination status; ensuring food security; reducing displacement; and prevention and treatment of HIV. Climate-specific interventions include gaining and disseminating knowledge about climate change and its effects; concerted and coordinated action in reversing the drivers of climate change; and political mobilization.

A productive way of looking at climate science is captured by Richard Levins and Richard Lewontin in *The Dialectical Biologist*, in which they state, "[t]he fact that the future might be like the past is what makes science possible, while the fact that the future might not be like the past is what makes science necessary."[8]

The Trump administration's attitude toward climate science appears to be best summarized in a statement from Budget Director Mike Mulvaney: "We're not going to be spending money on that anymore."[9] Funding for the Environmental Protection Agency (EPA) was to be reduced by 31%, under the first budget proposal of this administration, with substantial cutbacks also being aimed at the National Oceanographic and Atmospheric Administration, National Science Foundation, President's Emergency Plan for AIDS Relief, United States Agency for International Development, and the National Institutes of Health. The Fogarty International Center was slated for elimination by Trump's first budget proposal, but was saved by congressional action. Career scientists have left the EPA in droves, leaving it with fewer employees than during the time of the Reagan administration. Such changes will have a profound impact on our ability to effect necessary changes in energy use, and our ability to prevent or respond to health consequences of climate change.

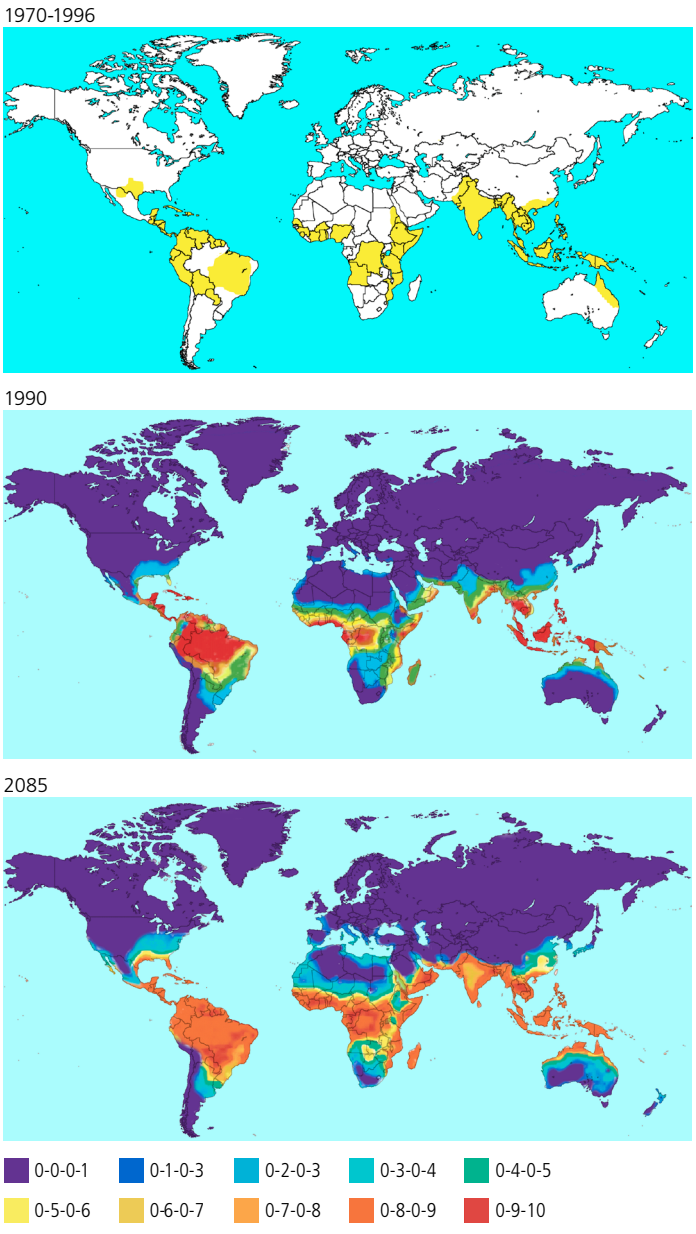


Figure 4. Top—Recorded outbreaks of dengue, 1970-1996. Bottom—Projected areas at risk for dengue, 1990-2085.[7]

With regard to concerted and coordinated action, we must strive for more prudent energy use. This requires personal and federal actions. On a personal level, if each one of us uses less energy per day, less heat will be generated, and that is a good thing. However, a great challenge at the individual level and the national level is what is known as the Tragedy of the Commons. This was an English observation (William Foster Lloyd, 1833) regarding the depletion of the commons occurring because each of several farmers considered only their own cattle's use of the shared land for grazing. We must realize that global risk is shared and overcome the urge to 'get our own piece while we can. Proactive steps must be put into place to deal with natural disasters and disease outbreaks. Through a lack of expertise and will, the administration's failure to reconstruct crucial infrastructure in Puerto Rico and the US Virgin Islands following Hurricanes Irma and Maria has left Americans living in these islands vulnerable to infectious diseases and morbidity from other causes. Proactive efforts to detect disease outbreaks and to anticipate natural disasters are critical responsibilites of competent government agencies.

Political mobilization in this area is crucial. Pressure must be brought to bear on such players as President Trump, Duke Energy, Koch Industries, Halliburton, ExxonMobil, Shell, EPA Director Scott Pruitt, and Secretary of State Mike Pompeo.

We who have been involved with HIV as patients, scientists, and healthcare professionals know how crucial research, practitioner, and especially patient mobilization has been to the enormous progress made in treating HIV. We practitioners have learned much from our patients in this regard. It is to be hoped that we all can come together with the same spirit and urgency to mobilize our society and our public servants to enact social and energy policies that may save us from some of the coming climate change.

For those wishing to learn more about climate change and health, the author recommends *Climate Change and the Health of Nations: Famines, Fevers, and the Fate of Populations* by Anthony J. McMichael with Alistair Woodward and Cameron Muir.[10,11]

Presented by Dr Schooley in May 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Schooley in May 2018.

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1. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2015. Available at http://www.icmje.org. Accessed April 4, 2018.

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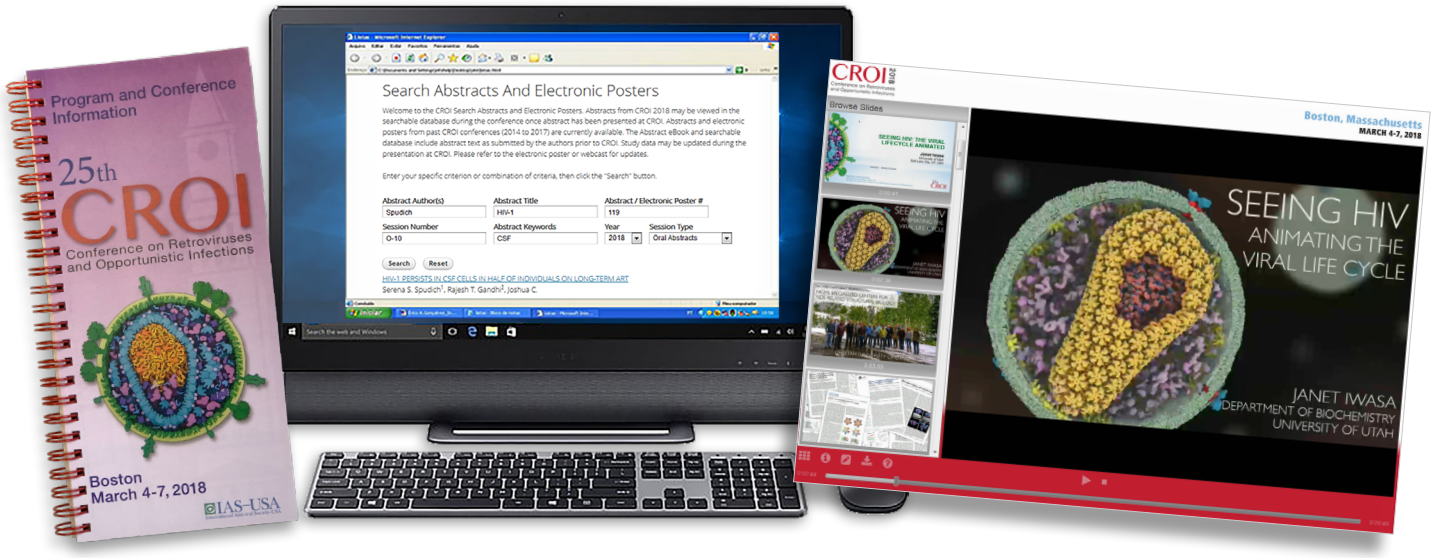

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