

A conversation with Anna Bershteyn on July 17, 2014

Participants

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Note: This set of notes was compiled by GiveWell and gives an overview of the major points made by Dr. Bershteyn.

Summary

GiveWell spoke with Dr. Bershteyn about diagnosis and prevention of infectious diseases in developing countries.

HIV/AIDS

Diagnosis

A variety of diagnostic tests are available for detecting HIV infection, the health of the immune system, and the effectiveness of drugs against HIV.

- A common approach to testing for HIV is to detect the antibodies that an infected person has developed against HIV. This can be done with tests that are inexpensive, fast to perform, and reliable except for in certain special situations. ELISA and Western blot tests can be performed in a laboratory. In resource-limited settings it is common to use a rapid test, which is a kit that does not require a specialized laboratory and provides a result in twenty minutes. Point-of-care tests are also available, which can detect HIV antibodies in blood or in the fluid around the gums, eliminating the need for a finger prick. Antibody tests are very accurate as long as performed according to instructions, but they have some limitations. It can take 6 to 12 weeks to develop antibodies specific for HIV, so the test can produce a false negative if used early in infection, a time called the “window period.” The test can produce a false positive in babies born to HIV-infected mothers, whose blood will contain the mother’s HIV antibodies regardless of whether the baby is infected. And individuals who have volunteered in HIV vaccine trials may have developed vaccine-induced antibodies while remaining uninfected. For these special groups, an alternative option is PCR-based testing for HIV RNA.
- Fourth-generation HIV tests can detect HIV earlier, and can distinguish early vs. chronic HIV infection. They probe for HIV antibodies and separately probe for the HIV antigen p24. The protein p24 is not detectable by the protein assay after host antibodies have developed against it. Therefore, having an antigen-reactive test is a sign of early HIV infection, while a positive antibody test is a sign of longer chronic infection.

- PCR-based tests detect the genetic material of HIV. These are recommended for diagnosis of infants under eighteen months born to HIV-infected mothers, and for individuals who have developed HIV antibodies during a vaccine trial. For those known to be infected and receiving treatment, PCR-based testing is used to determine how well the treatment is suppressing viral replication. Performing these tests on blood requires laboratory infrastructure and rapid, cold transportation of samples to the laboratory. The test can also be performed on dried blood, which extends the shelf-life and heat stability of the sample, but also makes the laboratory methods more complicated.

CD4 count

The CD4 count shows how much of a patient's immune system has been damaged by HIV. The following are the interpretations of various CD4 counts:

- Above 500 cells/uL: WHO recommends starting treatment, with higher priority given to patients with lower CD4 counts or other complications.
- above 350 cells/uL: usually asymptomatic, but the risk of TB is elevated.
- 200-350: elevated risk of TB; patient should be on treatment
- 200: elevated risk of many infections; very important for patient to be on treatment
- 50: average when patient dies without treatment, though this depends on TB and other factors.

CD4 testing is performed immediately after a diagnosis of HIV to determine how sick the patient is and whether the patient needs to begin treatment. Treatment reverses the decline of CD4 count (although CD4 rarely bounces back to the full level of a healthy person – the lower the CD4 at initiation, the lower it usually is after reconstitution on treatment).

There are some cases in which CD4 testing is bypassed and treatment is recommended immediately: if the patient has active TB, is a child (children progress to AIDS quickly), is pregnant, or has an HIV-negative partner.

CD4 testing is typically performed in a laboratory using an instrument that counts the number of CD4-expressing cells in the blood sample. Point-of-care tests exist in some settings, but their availability is limited. For the more common laboratory tests, the result is not returned during the patient's visit with the provider because of the time required to transfer the sample to the lab, run the test, and report back the results. Patients whose care decisions depend on CD4 count are generally asked to return on another day. A substantial fraction of patients do not return to continue with their care. More studies need to be done to understand why such patients do not return, and how long it takes for them to re-initiate care in the same or a different clinic, if they ever do. However, point-of-care CD4 testing alone does not appear to be a single magic bullet for keeping patients in care, because this question can be applied to virtually all stages of HIV testing, care, and treatment.

Dr. Bershteyn believes that, if not for resource constraints, the ideal health policy would be for everyone who is HIV-positive to begin treatment immediately. People who have a CD4 count of 500 do not need treatment, but if they begin trying to get on treatment when they are at 500, they can begin treatment before their count goes below 200. Moreover, young and sexually active adults tend to have higher CD4 counts for two reasons: because they are more recently infected than older adults, and because they have healthier immune systems so their CD4 declines more slowly. Thus, initiating people earlier maximizes the chance for treatment to suppress their infectiousness when they are most likely to pass on HIV to a new sex partner.

CD4 testing for the purpose of treatment initiation may become obsolete if early treatment is recommended in everyone regardless of CD4 count. It would still be needed as part of routine patient monitoring, but would be no more important than, say, monitoring of liver enzymes or whole blood count – just another standard part of routine bloodwork.

Viral load testing

The viral load is the number of viral copies per milliliter of blood plasma. Viral load is used as a proxy for how infectious the patient is and how quickly the patient's immune system is being destroyed. It is used to determine whether the treatment is working. It helps doctors provide immediate feedback to the patient and helps them know when to provide adherence counseling to patients and when to switch drugs due to drug resistance.

Many people are working on viral load testing. In South Africa, the National Health Laboratory Service (NHLS) has central laboratories for viral load testing. Dr. Bershteyn hopes that people can make viral load testing high-throughput and very cheap.

Médecins Sans Frontières (MSF) recommends scaling up viral load testing (<http://www.msfacess.org/sites/default/files/How%20Low%20Can%20We%20Go%20VL%20pricing%20brief.pdf>).

Some of the push for increased viral load testing is based on a paper that compared outcomes of people being treated for HIV in South Africa to people in Zambia. Even though people in South Africa begin treatment with lower CD4 counts, their survival is better than that of people in Zambia. Of course, there are other important differences that contribute to HIV survival, so this research is not definitive.

Tuberculosis

Diagnosis

The difficulty and cost of diagnosing TB is a huge problem that needs solving. GeneXpert is one expensive solution that has improved TB diagnosis. An ideal diagnostic would be rapid, inexpensive, and operate on a sample that is easy to collect and safe to handle.

Treatment

Another huge problem is development and optimization of antibiotic regimens for TB. People with TB often cough and spread TB for some time before getting diagnosed and receiving treatment. Improper treatment with drug courses that do not contain all of the necessary drugs, are too short, or are not adhered to properly, can lead to the development of drug-resistant TB. Drug-resistant TB can be spread to others, so a person can end up with drug-resistant TB by not completing a treatment regimen, or by catching drug-resistant TB from another person. So far, a majority of TB cases are sensitive to first-line therapy.

From a public health perspective, the priority needs to be more rapid and accurate diagnosis, rapid initiation of treatment, and adherence to the full course of treatment. This can help prevent the spread of TB and also prevent the evolution of drug-resistant TB. Epidemiologists estimate that the most efficient way to fight drug-resistant TB is to prevent it by improving treatment quality in people who are at risk of developing resistance.

From a human rights perspective, it is also important to consider that second-line therapy (or third-line, and so on) for drug-resistant TB is extremely expensive, and the drugs have serious side effects. One interesting resource to browse is “An Activist’s Guide to Tuberculosis Drugs,” which lists TB drugs and advocacy routes related to TB treatment, such as encouraging pharmaceutical companies to lower the price of a certain drug or direct research at refining the dosage of a drug to reduce its side effects.

(<http://www.treatmentactiongroup.org/sites/g/files/g450272/f/201406/An%20Activist's%20Guide%20to%20Tuberculosis%20Drugs%20V9.pdf>)

Vaccines

The BCG vaccine partially protects children from TB. Innovation is needed toward the development of effective and durable TB vaccines.

Sanitation

Many hobbyist philanthropists have invented DIY water purification systems, but it is difficult to get people to use them if many steps are required for purification.

Maternal and child health

Breastfeeding

Breastfeeding is important in resource-limited settings because it protects infants from pathogens in the water supply, and because it offers additional protection through the mother’s antibodies, lactoferrin, and other active molecules in breast milk. There are advantages to beginning breastfeeding immediately after birth, to help expel the placenta and stop the bleeding. The first three days of breast feeding are the most important, because that is when most of the antibodies are transferred. It is too expensive to produce formula that contains the antibodies that are naturally found in colostrum. If a mother is using formula mixed with local water, it is important to ensure that it is a safe water source.

Pathogens can be killed by boiling, but there are other risks to consider as well. For example, excessive fluoride is bad for infants, which is a consideration in places where over-fluoridation can happen by accident in less well-regulated water systems.

Most new mothers will say that breastfeeding is challenging. There are techniques for breastfeeding that mothers may not know. Psychosocial and medical support is especially needed in conflict areas where women have been subjected to abuse, and in places where breastfeeding is was not practiced by older generations who are now mentoring new mothers.

Hypothermia

Hypothermia is an important issue in neonatal health. In some cultures it is customary to wash newborns immediately after birth. There is a risk of hypothermia, as well as a potentially increased risk of infections because newborns are covered in a substance called vernix that has antimicrobial properties. The newborn should be placed on the mother skin-to-skin and encouraged to nurse, with a blanket covering both of them. The umbilical cord should be cut with a sterilized instrument.

Infection control at birth

This is another topic that should be on GiveWell's list.

Vaccines

There are several vaccines that are now available in first world markets, that could really have a big impact in third world settings. These include rotavirus (the main cause of childhood diarrhea, which is a leading killer of babies), HPV vaccines (against the virus that causes cervical cancer), pneumococcal vaccines, and others.

A major funder of childhood vaccines for poor countries is GAVI alliance. GAVI pays for a 5-in-1 'pentavalent' vaccine in all 73 of the world's poorest countries.

The pentavalent childhood vaccine protects against these five diseases: diphtheria-tetanus-pertussis (DTP), hepatitis B, and Haemophilus influenzae type b. There is work underway to look into incorporating more of the above vaccines into a hexavalent (or more) childhood vaccine, but there are technical and cost-related challenges.

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