



Pulmonary Hypertension and HIV

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People living with HIV have long had enough to worry about from the most common opportunistic infections and HIV-related conditions. There are, however, a number of less well-known illnesses for which HIV is considered a risk factor. When people afflicted with these conditions turn to general sources of HIV information, they often find little or no recognition of the connection with HIV. Consequently, they often feel isolated and alone in facing their new problem and can't get much help from their usual support mechanisms.

One such illness that recently came to Project Inform's attention in a dramatic and personal way is called PH, short for Pulmonary Hypertension. Though hypertension (high blood pressure throughout the circulatory system) is a common illness, PH is a relatively rare condition. It is distinguished by high blood pressure in the pulmonary artery, the main blood vessel that carries blood from the right ventricle (chamber) of the heart to the lungs. It is typically a progressive disease that ends in death if untreated.

The general cause of this increased blood pressure is a thickening or constriction of the pulmonary artery and the smaller blood vessels in the lungs that branch out from it. In a person with pulmonary hypertension, the branches begin to close off as the blood vessels thicken, starting with the smallest vessels first. As more and more branches close down, the lungs produce less oxygenated blood and the body becomes starved for oxygen. This causes the right ventricle of the heart to work furiously, trying to force more blood through the lungs to get more oxygen to the body. It is not designed for such high pressure work and the muscle soon stretches and eventually leads to congestive right heart failure, a type of heart of attack and potential cause of death.

Symptoms of PH

The most obvious symptoms of PH are shortness of breath, dizziness, fatigue, swollen ankles, poor lung capacity and sudden fainting or loss of consciousness due to inadequate intake of oxygen for the brain. The process begins slowly and most people have the disease for a few years before getting a correct diagnosis because the early symptoms are similar to those of many other diseases. The diagnosis is made *differentially*—that is, by ruling out other causes. The disease is progressive for two reasons. (1) The underlying cause remains present despite treatment; and (2) the rising blood pressure in the lungs increases the speed at which blood must flow through the remaining open blood vessels, causing friction on the cells of the inner lining of the vessels, further thickening them, resulting in ever more constriction.

The symptoms of PH somewhat resemble those of asthma, a common lung disease that also results in poor oxygenation through the lungs (though by a different mechanism). A person with PH, however, does not experience the "wheezing" typical of asthma, since the problem is due to a lack of oxygenated blood, not a problem getting air into the lungs. Many types of heart disease can also produce symptoms that resemble PH as well.

One prominent PH specialist has likened PH to "a slow death by drowning." The progressive inability of the lungs to supply oxygen can greatly restrict a person's activity levels and lead to increased isolation. Although a person with PH might feel fine while sitting, a simple climb up out of a chair or a short walk can trigger shortness of breath, dizziness or even a blackout. Patients quickly lose confidence in their ability to cope with even the most basic daily activities. Without treatment, many people become housebound and in need of oxygen tanks and masks. Doctors discourage air travel due to the reduced cabin air pressure and lower oxygen levels maintained on commercial airliners, which further exacerbate the problem.

PH must be diagnosed by an experienced cardiologist (heart specialist), pulmonologist or a PH specialist. A similar level of experience is needed to treat the disease.

PH and HIV

No one knows for certain what the mechanism or link is that connects PH with HIV infection, even though inflammatory cytokines, which are common in people with HIV, are suspected as one of the possible causes. HIV been shown to be an independent risk factor for PH. Chronic hepatitis B and C, which are relatively common co-infections with HIV, are also risk factors for PH, but they explain only a small portion of the incidence of PH among HIV-positive people.

PH was originally believed to be a disease primarily affecting women but more recent findings seem to show a more widespread



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distribution among women and men. It is possible that the link to HIV is changing the makeup of the PH population. Other researchers simply believe that we are still in the early learning stages about PH and do not yet have a full picture of who gets it and why.

Two recent studies concluded that the incidence of PH in HIV-positive people is about 1 in 200, as compared to 1–2 cases per million yearly in the general population. This means the risk of PH is several thousand times greater for HIV-positive people than the general population. It is also likely that at least some HIV-positive people whose deaths have been attributed to heart disease, particularly congestive heart failure, were preceded or caused by PH. Several years ago, Paul Corser, an early and well-respected AIDS activist who worked at amfAR until his death, struggled with PH in his final years. More recently, an HIV-positive Project Inform board member was diagnosed with PH. Her struggle led to this article's effort to better inform the HIV-positive community about this illness.

Treatment for PH

Until recently, the only treatment available for PH was a GlaxoSmithKline drug called epoprostenol (Flolan). It offers a mixed bag of benefits and drawbacks. It usually works quite well, reversing most symptoms for a considerable period. But it comes at a high price in terms of side effects, quality of life and cost. The drug must be directly delivered into a vein (intravenous infusion, IV) 24 hours per day. This means patients must have a surgically implanted IV (Hickman) line and carry a continuous infusion pump for the rest of their lives. Having an IV line carries risks of severe and life-threatening infections, notably sepsis. The drug is not a cure and works only as long as it is continued. It is extremely expensive, ranging from \$50,000–\$100,000 per year, depending on dosage, plus additional costs for the pump, IV lines, etc. As an "orphan drug" (a drug for a relatively rare disease that affects less than 200,000 people annually), these costs are not unusual.

In the fall of 2001, a new, simpler oral drug, bosentan (Tracleer) was approved by the FDA. Bosentan, a tiny pill taken orally twice daily, works by a different mechanism than epoprostenol. It is made by a Swiss company, Actelion, and distributed in the US by Genentech of northern California. While bosentan doesn't work in every case and may not be adequate in advanced disease, its greater simplicity and consequently better quality of life make it a godsend for many people with PH. It appears to at least halt disease progression within 30 days in most people and improves oxygen flow in many. Fortunately, the mechanism of action of bosentan is believed to be the most relevant mechanism for HIV-associated PH.

People using certain HIV antivirals, specifically ritonavir, need to exercise caution when using bosentan because of possible drug

interactions. These interactions have not yet been tested, but it seems likely that ritonavir may increase the blood levels of bosentan, leading to an increased risk of liver-related side effects. Although studies combining bosentan and epoprostenol have not yet begun, there is interest in pursuing this because of their different mechanisms of action. Combination therapy, in this case, would eliminate the quality of life advantages offered by bosentan, but an oral formulation of epoprostenol is in development.

Project Inform encountered a slightly bumpy road in pursuing access to bosentan for HIV-positive people. Well before the drug was approved, it was available on an expanded access basis to people with PH, employing the regulatory mechanisms fought for and won by AIDS activists in earlier years. But in this case, the expanded access program excluded HIV-positive people, on the grounds that the new drug had not yet been specifically tested in HIV-positive people. HIV-positive people had also been excluded from the studies used to license the drug. There were also concerns about interaction with HIV antivirals.

Project Inform, which has played a fundamental role in creating earlier access programs for drugs, responded with a ferocious burst of activity. Through appearances at an FDA Advisory committee, pressure and support from the FDA, and hastily called meetings with company officials and clinical investigators, the ban on access for HIV-positive people was lifted just ten days after we first became aware of it.

For more information on support resources, or referral to PH research sites, call Project Inform's Hotline.

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