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Rapid Testing Stalled

By Bob Huff

An article in *The Los Angeles Times* recently reported that seven babies in the region had acquired HIV at birth. The children had been infected at varying times during the past few years but had not been identified sooner because California does not routinely test newborns for HIV. Not surprisingly, most cases of transmission involved women who had declined to be tested for HIV during their pregnancies or had not received prenatal care. Dr. Jonathan Fielding, Los Angeles County's director of public health confirmed that, "Those most at risk of not receiving prenatal care—including HIV tests—include women who are drug addicts, incarcerated, homeless, non-English speakers, undocumented immigrants, uninsured or teenagers."

Why are rapid HIV tests that are available in Japan, France and Thailand unobtainable in the U.S.?

It's known that transmission of HIV to infants is largely preventable with either a course of AZT as a part of prenatal care or with a single dose of nevirapine administered prior to or during labor. Even a single nevirapine dose to the baby if given within 24 hours of birth may prevent infection from taking hold. Antiretroviral therapy can reduce the newborn infection rate from as much as 50 percent to less than 8 percent (what happens next is a different problem: See *HIV & Breastfeeding* in this issue). In parts of the world with high HIV prevalence and limited resources for prenatal care and testing, some have proposed offering nevirapine to every mother as she enters labor since the drug is cheaper than the test. But in areas with low rates of HIV incidence, knowing the HIV test result prior to delivery is essential to identify everyone who can be helped by treatment.

In Los Angeles, at least one of the HIV-positive infants was not treated because test results were not received in time to alert the medical staff. With conventional tests, a lag of up to four days between the time blood is drawn to when the results are known leaves the door open for preventable infections to slip through. Dr. Andrea Kovacs, chief of the Los Angeles County-USC Medical Center's program for HIV-positive women, children and adolescents was quoted in *The Times* article as saying rapid testing could have provided results within an hour. "We would have treated the baby if we knew the mom was HIV-positive."

Rapid tests for HIV perform the same job that standard laboratory-based HIV tests do—but faster. Currently, before a definite diagnosis of HIV infection can be given, an initial positive result with either the rapid or conventional test must be confirmed with another type of laboratory-based HIV test called the "Western Blot." But in situations when labor has already begun and there is

no time for laboratory confirmation, a positive rapid test result may justify offering the mother and child nevirapine treatment. The convenience of rapid testing, however, does not preclude the need for pre-test informed consent and post-test counseling.

There are more than a dozen rapid HIV tests on the market throughout the world and simple one-step tests are the norm in regions without expensive laboratory resources. But in a strange twist on the usual story of the Haves and Have Nots, no easy-to-use rapid HIV tests have been approved by the FDA for use at the point of care in U.S. hospitals, clinics and testing centers. The single one-hour test that has been approved still depends on laboratory processing and expert interpretation.

Anyone who wants to market an HIV test that detects both HIV-1 and HIV-2 in the U.S. needs the permission of Abbott and the others.

The potential demand for a rapid HIV test in the United States is huge. Rapid tests cost no more than conventional tests and the FDA has recently indicated that confirmation of a positive rapid result with another type of rapid test may be an acceptable substitute for confirmation by Western Blot. (See *Rapid New World* for how this problem is handled elsewhere in the world.) Providers of HIV counseling, testing and referral services are also anxiously waiting for point-of-care rapid testing. Statistics show that up to a third of people who have a sample taken for conventional testing never return to get their results. Point of care testing promises to be far more cost effective than conventional testing because fewer tests will be wasted on no-shows. In addition, prevention experts are eager to find ways to reach those most at risk for slipping through the cracks of existing counseling and testing services that require follow-up appointments.

So why are rapid HIV tests that are available in Japan, France and Thailand unobtainable in the U.S.? The answer seems to be because the big companies that make the conventional tests don't want the competition. And because of a complicated web of patents and intellectual property agreements, these corporations have the clout to keep rapid testing out of the established $200 million per year U.S. market for laboratory-based tests.

According to a recent article in *The Wall Street Journal*, the problem stems not from testing for HIV-1, the most common HIV infection in the world, but with patents that cover testing for HIV-2, an AIDS-causing virus most prevalent in West Africa. Although HIV-2 infections have been reported in areas with large immigrant populations such as New York, overall, infections with the "other" HIV are rare in the U.S. When a test for HIV-2 became available in 1990, the Centers for Disease Control, the federal agency responsible for the safety of the national blood supply, recommended that HIV blood-screening tests should be able to detect both types of HIV. Although the FDA requires that blood-screening tests check for HIV-2, the agency does not ask the same of tests used to diagnose HIV in individuals. Yet producers of HIV diagnostic assays have voluntarily adopted the standard that an HIV test should be able to test for all forms of HIV prevalent in the world.

The patent for the HIV-1 test is controlled by the U.S. National Institutes of Health (NIH). The NIH has freely issued permission to use the patent in exchange for modest royalty payments which are shared with the French Institut Pasteur, a co-discoverer of HIV-1. Several years after the first test for HIV-1 became available, researchers at the Institut Pasteur learned that HIV-2 could also cause disease and that the existing HIV test could not reliably detect it. The Institut Pasteur received a comprehensive U.S. patent for HIV-2, which was then licensed to a spin-off, for-profit corporation. In a complicated series of business transactions, effective control of the U.S. patent was subsequently traded among the big-three makers of conventional diagnostics, including Abbott Laboratories, the largest supplier of HIV tests. The result: anyone who wants to market an HIV test that detects both HIV-1 and HIV-2 in the U.S. needs the permission of Abbott and the others.

Several makers of rapid assays that detect both HIVs have tested the waters for U.S. approval. Most have received positive signals about their chances. Yet in every case, failure to come to terms over the HIV-2 patent has sunk efforts to bring these tests to market. According to *The Wall Street Journal*, one company, Universal Healthwatch, attempted to license HIV-2 but was stonewalled by the patent holder. The company, afraid to risk a lawsuit over an alternative method for detecting HIV-2 and unwilling to offer a product that only tested for HIV-1, abandoned the campaign. Until recently, a rapid test called OraQuick that had been successfully used by the CDC on an experimental basis seemed poised for FDA approval. When the company realized it would not be able to obtain a license to use the HIV-2 patent in the U.S., it tried a different tack. Abbott was approached about distributing OraQuick under their license for HIV-2, yet the diagnostic giant would not agree to guarantee minimum yearly sales of the test. According to *The Journal*, the OraQuick executives feared that Abbott was only interested in obtain-

ing the rights to their product as a ploy to keep it off the market.

In 1999 ownership of the HIV-2 patent with all of its encumbrances passed to Bio-Rad Laboratories, a California corporation. Bio-Rad claims that it has since entered into HIV-2 licensing agreements with numerous companies, yet suggests that, when it comes to the U.S. market, its hands are tied by the inherited obligations to Abbott and the others. In a letter to GMHC, David Schwartz, president of Bio-Rad said, "We evaluate each request on a case-by-case basis and enter into licensing agreements based on a variety of criteria, some of which we are obligated to maintain as a result of our acquisition of ... the HIV-2 patent."

The frustration over the deadlock is evident in a statement quoted by *The Journal* from Bernard Branson, who heads the CDC's HIV diagnostics program. "I'd call it restraint of trade. It's a travesty to stand by and allow these tests to languish." Reportedly, the CDC has asked the Justice Department to investigate if BioRad and its partners have violated antitrust laws.

Faced with this stalemate and with clamor from the prevention community for rapid testing, the FDA last year finally gave a clear signal that diagnostic products that tested for HIV-1 alone would receive a favorable review as long as trial data demonstrated performance comparable to lab-based assays. Reportedly, this has unlocked the gates and several rapid test makers have submitted applications to the agency. It's possible that an approval could be seen later this year. As for HIV-2, the patent expires in 2010.

Rapid Tests in Use

Independently evaluated rapid HIV tests with promising performance.

Easiest to use: May be suitable for point of care.

Determine HIV-1/2/O	Abbott
OraQuick	Epitope, Inc.
Hema-Strip HIV-1/2	Saliva Diagnostic Systems
UniGold HIV-1/2	Bray

Requires additional laboratory processing: Suitable for clinics.

Retrocell HIV-1/2	Abbott Laboratories
SUDS HIV-1	Abbott Laboratories
SimpliRED HIV-1/2	Agen Biomed
MicroRED HIV-1/2	Agen Biomed
Bionor HIV-1/2	Bionor A/S
Genie II HIV-1/2	BioRad Laboratories
Multispot HIV-1/2	BioRad Laboratories
Red Dot HIV-1/2	Cal Test Diagnostics
Serodia HIV-1/2	Fujerebio
HIV SPOT-1/2	Genelabs Technologies, Inc.
HIV SAV-1/2	Sayvon Diagnostics, Ltd.
Entebe HIV Dipstick	Hepatika Laboratories
Dipstick HIV-/2	Immunochemical Laboratories
HIV Tri-Dot	J. Mitra & Co.
MedMira HIV-1/2	MedMira Laboratories
DoubleCheck HIV-1/2	Orogencis Ltd.
HIVCHECK HIV-1/2	Saliva Diagnostics Systems
Sero-Strip HIV-1/2	Saliva Diagnostics Systems
CombAIDS HIV-1/2	Span Diagnostics
Capillus HIV-1/2	Trinity Biotech
SalivaCard HIV	Bray
SeroCard HIV	Bray
Quix HIV-1/2/O	Universal Healthwatch
DIA HIV-1/2	Weiner Labratorios

Source: Rapid Tests for HIV Antibody, Bernard M. Branson; AIDS Reviews 2000;2:76-83

Rapid New World

By Bob Huff

In the U.S., the gold standard for diagnosing HIV infection has evolved into a formal process that respects an individual's need to know the facts about HIV: how the virus is transmitted, how to limit one's risk, and the meaning of a positive test result. The process also respects an individual's privacy and strives to provide appropriate counseling and support if a test result is positive. The system is also careful to confirm that a positive result is truly positive to avoid falsely telling someone they have HIV.

When the healthy immune system is exposed to HIV antigens (antigens are bits of the protein structure of the virus), it will produce proteins called antibodies that stick to the viral particles and help clear them from the body. That HIV ultimately evades this system is why the disease is so serious. HIV tests use artificially produced HIV antigens that can capture antibodies if they are present in a person's blood. If a person has never been exposed to HIV, then no antibodies will stick to the antigen in the test and it will read negative. But if the antibody test is positive, it means that the person has had an immune reaction to HIV in the past and is probably infected. These tests are called immunoassays.

For a test to be sensitive enough to detect 99.9 percent of positive samples, it may sometimes read positive when no HIV is present.

The usefulness of an HIV antibody test is judged by its sensitivity and specificity. Sensitivity is the ability of a test to detect HIV even when present in very small amounts. If a test is not sensitive enough, some positive samples will slip though the screen. But for a test to be sensitive enough to detect 99.9 percent of positive samples, it may sometimes read positive when no HIV is present. This is called a false positive result. The other measure of a test's reliability is its specificity. This tells how well the test discriminates between detecting HIV and other somewhat similar antibodies. There is usually a tradeoff between sensitivity and specificity, with highly sensitive tests being more likely to be fooled into giving a false positive answer by similar but non-HIV antibodies.

The trade-off between sensitivity and specificity is why a positive result on an initial HIV test must always be confirmed with a second, more specific, HIV test before telling someone they are positive. Highly sensitive tests are ideal for jobs such as screening the blood supply or performing anonymous surveillance of HIV prevalence in a population. In particular, blood screening is a job where it is better to be safe than sorry; a few false positives are not of concern. But a positive HIV diagnosis is of huge concern to the person who gets one, so the system is careful to be sure the diagnosis is correct.

Rapid testing brings a new challenge to the established system of confirming a diagnosis before telling someone his or her results. If a simple finger prick device can give a result within 15 minutes (similar to a home pregnancy test), how does a test provider deal with a positive result? One way is to tell individuals that they have had an inconclusive result then draw more blood to send to a lab for the conventional test and confirmation process. So while a single rapid test may be fine for alleviating the anxiety of the uninfected, it may not be the best solution for someone who really has HIV.

In parts of the world where conventional laboratory-based tests are often not available, a number of rapid tests have come into common use over the past decade. The World Health

WHO Algorithm for Confirming HIV Diagnosis with Rapid Testing

Objective		Prevalence	Strategy
Blood Screening		All	1
Surveillance		10%	1
		<10%	2
Diagnosis	With symptoms	>30%	1
		<30%	2
Diagnosis	Asymptomatic	30%	2
		<30%	3

Strategy 1: Single screening assay. Reactive test is considered positive.

Strategy 2: Two screening assays. If initial test is reactive, test is repeated with second assay. Specimen considered positive only when both assays are reactive.

Strategy 3: Three screening assays. Specimen considered positive only when all three assays are reactive.

Organization (WHO) has developed a set of protocols for using combinations of rapid tests to deliver reliable, confirmed results, depending on the purpose and context of the test.

The result is a system capable of providing test results with the same confidence as laboratory-based testing but at a far lower cost. In addition, the availability of same-day results means that many more people learn their HIV status and remain available for counseling about their health. Studies have shown that people who learn their diagnosis are more likely to begin practicing risk reduction behaviors than those who fail to return for their results.

The WHO protocol recommends confirmation with multiple different rapid tests depending on the objective of the test and the background prevalence of HIV in the region. A single test may be sufficient for screening blood or performing surveillance studies in high prevalence regions. For individuals with symptoms of HIV disease living in a high prevalence area, a single test may also suffice. In areas with a lower background prevalence of infection, the proportion of false positives from too-sensitive tests demands additional confirmatory testing.

In settings where multiple confirmatory tests are expected, the first test performed should have very high sensitivity to insure that all true positives are captured. Since these first pass tests will tend to report a higher number of false positives, the second, confirmatory test should be highly specific for HIV. In multiple test systems, each test should use a different antigen to avoid overlapping specificity. One drawback to rapid assays is that a new sample may need to be obtained if an individual requires a confirmatory test. WHO recommends collecting serum, plasma or dried blood spots if multiple test strategies are used, to avoid having to collect multiple samples.

A Comparison of HIV Testing Technologies: Immunoassays and Rapid Tests

HIV Testing Technology	Specimens	Advantages	Limitations	Cost[a] (USD)	Complexity[b]
Conventional EIA	Serum Plasma Dried blood spots Oral fluids Urine	• Can be batched: good for ≥100 specimens at a time • Can be automated • QA/QC done at national and regional laboratories: easier to control • Cost per test less than cost per rapid test • Identifies seroconverters earlier: highly sensitive, which reduces non-reactive period	• Not flexible in testing (need minimum numbers filled) • Requires skilled, trained technicians to perform and read test results • Requires >2 hours for results (if need to run two EIAs, >5 hours) • Requires special equipment • Requires maintenance of equipment • Reagents must be refrigerated	1–2	4
Rapid test	Serum Plasma Whole blood Oral fluids[c]	• Good for testing 1-100 specimens at a time • Requires minimal equipment and reagents • Can be performed in a clinic (on-site testing) • Highly skilled staff not required • Very easy to interpret test • Results in >45 minutes • Test kits can be stored at room temperature (increased stability)	• Not good for testing >100 specimens at a time • The QA/QC is performed at multiple sites; requires more control • May cost more per individual test than EIA • Choice of testing strategy may require multiple specimens • Interreader variability may provide inconsistent results with some assay formats (e.g., particle agglutination)	1–3	For tests based on: Immuno-chromatography[1] Dipstick and membrane flow-through technology[2] Agglutination[3]

[a]The cost of a testing technology will be affected by the direct and indirect costs. [b]UNAIDS/WHO's four categories of complexity for HIV antibody tests: 1) No additional equipment or laboratory experience is required; 2) Reagent preparation or a multistep process is required; 3) Specific skills such as diluting are required; and 4) Equipment and trained laboratory technician are required (UNAIDS/WHO 1998). [c]Rapid tests using oral fluids are under evaluation in field settings.

EIA=enzyme immunoassay; QA/QC, quality assurance/quality control.

Source: Guidelines for Using HIV Testing Technologies in Surveillance: Selection, Evaluation and Implementation. UNAIDS.

Patent Primer

By Bob Huff

Ideas aren't real estate. But when ideas and technical know-how are protected by a legal creation known as a patent, they become a temporary kind of property. Patented ideas are often referred to as intellectual property, a class that also includes copyrights and trademarks. Like other forms of property, intellectual property can be sold, traded, misused and defended in court.

In the world of patent law, new knowledge about how to make or use some form of matter is called an invention. Individuals who believe they have invented something useful can ask the government to decide if their idea is sufficiently different from similar previous inventions that it should receive patent protection. A patent simply grants the legal right to stop other people from using the invention for commercial gain for a period of time—20 years in the U.S. If granted a patent, an inventor can market the product or process for his own profit, sell or assign the right to do so, or license the right to third parties.

The costs associated with the discovery of an invention leading to a patent are typically only a small part of the expense of bringing a drug product to market.

Under U.S. law, a patent gives the inventor the "right of exclusion," that is, the right to prohibit others from using their invention. This is a limited right and doesn't mean that just any invention can be marketed. For example, someone may invent and patent a new kind of poison, but the patent gives him no right to make and sell poison outside of the usual restrictions that apply to the sale of poisons. The patent only grants a right to try and stop anyone else from making and selling that poison within the U.S.

The first step to obtaining domestic patent protection for an invention is to have it evaluated by an examiner from the U.S. Patent and Trademarks Office. The examiner compares the invention to earlier, similar, inventions and tries to determine if three tests are met: The invention must have some kind of use, it must be substantially new or represent an improvement on earlier inventions, and it must not be "obvious." A claim on the use of water for human hydration (drinking) is an example of an obvious use of water and therefore not patentable.

Since patents are legal grants by the government, they are not absolute. In the same way that government can take someone's real estate in order to build a new road or other public amenity, the rights to an invention can be denied or reassigned in the interests of national security. For example, no invention pertaining to atomic weaponry may be granted a patent—it automatically becomes the property of the government.

Companies that depend on innovation to give them an edge in the marketplace use patents to help protect their investments. Enterprises are more confident about spending money to develop new ideas into products if they are assured that they have a legal right to stop others from using their inventions. Patents limit the risk of developing new products by guaranteeing the patent holder a competition-free head start to recoup costs and hopefully make a profit.

Patents are used to protect investments in all phases of product development, not simply to reward the discovery of an idea. Although patents are granted to individual inventors and recognize authorship, they only take on economic value when a company is willing to launch a commercial exploitation of the invention. The economic value comes from the assurance of a guaranteed period of market exclusivity. Typically, companies that employ researchers and engineers contractually require their employees to assign any patents they obtain to the corporation. Often a product will be protected by more than one patent on more than one of its novel aspects.

Patents are considered particularly crucial to pharmaceutical manufacturers. Extended periods of protection are sought since it may take several years after a patent is granted for a new drug to be thoroughly tested and proven safe and effective enough to sell. Long periods of market exclusivity after approval allow companies time to recover development costs for the approved drug, absorb costs for unsuccessful attempts, support the development and marketing of new drugs, and generate profits. The costs associated with the discovery of an invention leading to a patent are typically only a small part of the expense of bringing a drug product to market.

After a drug patent expires, manufacturers of generic medicines are free to begin making and selling an approved equivalent version of the drug—usually at a substantially lower price based on the actual cost of making and distributing the drug. Although some kinds of products are able to retain brand identity and market domination even after patent protection has expired, in the pharmaceutical industry the potential to generate revenue from an unprotected drug is cut drastically. Insurance companies,

HMOs and other payers often opt for the cheaper generic version of a medicine as soon as it becomes available.

Because patent protection is a legal device, it is dependent on governments to grant, adjudicate and enforce. Worldwide, patent laws have varied considerably, with some countries respecting U.S. and European patents explicitly, others limiting what kind of inventions can be patented or for how long they should be protected, and other countries offering no protection at all. Often a company will not seek patent protection in a country in which it perceives no market potential. Recently, in an effort to stabilize the worldwide business climate, proposed new international trade agreements have insisted that all participating countries establish patent laws in conformity with those in the U.S. and Europe. One consequence of this has meant that some countries are faced with adopting unfamiliar legal concepts of property, which may result in the disruption of certain evolved business practices particular to weak economies. Yet signatories to the international agreements are given little leeway—they must accept international corporate conventions or face exclusion from the world economy.

Some countries with longstanding systems of patent protection for most inventions treat pharmaceutical products as a special category. In India, for example, foreign drug makers have not historically been offered market exclusivity for their medicines themselves—only for the methods of making them. This exception has allowed a vigorous market to flourish for domestically produced generic versions of drugs that had been developed and patented elsewhere. For a poor, highly populous country with ambitions of economic independence such as India, this accommodation has supported development of technical infrastructure, provided jobs and supplied medicines that would have been otherwise unaffordable.

Patent protections may be lacking altogether in other, less developed, countries. In the case of pharmaceuticals, though, since there may be no domestic capacity to produce drugs and few individuals affluent enough to afford them, the absence of protection in these countries has had little consequence for patent holders doing business elsewhere in the world.

Independent Review

By Carlton Hogan

There are certain minimum protections designed to help assure the integrity of research data that one should look for when evaluating reports of clinical trial results. There should always be several layers of review evident that not only evaluate the final result, but monitor the trial from initial design all the way through publication. In each of these, independent review is perhaps the most important common thread.

Institutional review boards

One of the first levels of review evaluates a research plan before it is implemented. Institutional Review Boards (or IRBs) exist at the actual sites in the communities where trials are undertaken. A typical IRB would include physicians, ethicists, members of the clergy, and patient representatives who assure that a trial will be appropriate and ethical within the culture of that particular community, and that limited resources are expended on questions that are relevant to that community.

Community advisory boards (CAB)

CABs are patient advisory groups drawn from the communities in which the trials will be conducted. They give the patient's perspective on whether a trial offers ethical, reasonable approaches to the issues that are relevant to that community. The federally-funded clinical trial networks such as the CPCRA or the AACTG are mandated to establish CABs. Each local CAB also elects one or several members to serve on a network-wide Community Constituency Group (CCG). This system of representation tries to insure that the medical and administrative leadership of the national networks will hear the concerns of community members that their research is supposed to benefit.

It was not always this way. Up until the late eighties, meetings of federally-funded AIDS research groups were closed affairs—patient representatives were not even welcome as observers. Courageous and brash activists crashed the group meetings of the AACTG (then called simply the ACTG) and demanded not only to observe the meetings, but also to participate in decision-making. Fortunately, some investigators were wise enough to see that community input could only help to create more relevant and attractive trials. It is now mandated in grants and cooperative agreements that federal-

ly-funded AIDS research groups not only have functional CCGs, but that patient representatives and other advocates be full members of key committees and protocol teams. Frequently the CCG representative will be listed among the group's research paper authors, thus helping assure responsible oversight from a patient perspective.

Data and safety monitoring boards

Every trial in the U.S. is overseen by what is called a Data and Safety Monitoring Board or DSMB. These are physicians, researchers and ethicists who have ongoing access to the trial data and are empowered to make important suggestions to modify, prolong, or even terminate a study, depending on what occurs in the course of that trial. If it becomes absolutely clear that one treatment is superior to another, the DSMB can choose to end the trial, so as to reduce the amount of time patients remain on the "loser" therapy. Alternatively, if they decide that a trial has no possibility of ever achieving a meaningful answer, they may decide to halt the study and stop wasting resources and participants' time. Or they may modify a trial to improve its scientific integrity or assure patient safety. A good example of this was an early AIDS trial of a drug called pyremethamine that depleted B vitamins. A DSMB decided that a special form of B vitamin called leucovorin needed to be added to the protocol to protect patients.

If you want to critically evaluate a research article, it's reasonable to want to know if the investigator had a financial stake in the outcome.

In general, while a trial is ongoing, very few people have access to the data. Usually only the statistician(s) and DSMB get full summaries of key endpoint data. Even the principal investigator is unable to review the data in midstream. This is to ensure that no one jumps to conclusions about trends seen in a trial that are not yet statistically significant (like trying to figure out the average number of coin tosses after only three flips) Otherwise there is a risk that the investigators or others could consciously or subconsciously alter their behavior, and affect the trial's outcome. The investigators are said to be "blinded" to the endpoint data. The DSMB also tries to strike a balance between closely watching the trial, and not looking too frequently. The reason for this is actually pretty simple: every time anyone takes a look at the data, they increase the risk of prematurely declaring a winner, when in fact, not enough data (or "coin flips") have accumulated to really be certain. So when the sample size (the number of patients) is calculated for a trial, it is adjusted upward for each time the DSMB is expected to take a peek.

Because the DSMB is privy to such sensitive information, it is absolutely imperative they be as independent as possible. If premature "hints" about how a trial is going leak into the community it could cause people to make up their minds even though the data are not yet reliable. So an independent DSMB is an absolute necessity for credible research

Disclosing financial ties

In all of these cases—IRBs, CABs, CCGs and DSMBs—the essential characteristic is that they be independent of the company making the drug and the organization conducting the trial. Independent reviewers must have no personal financial, ideological, or ego investment in the outcome of the trials they oversee.

These independent review mechanisms also protect investigators who often do have financial and other ties to corporations keenly interested in the outcome of the research they conduct. For better or worse, these financial relationships are now so common as to seem unavoidable. Therefore it is crucial that investigators disclose these relationships whenever writing or speaking about their research or offering their expert opinion on matters that could affect the business of their patrons.

Marcia Resnick, the former editor of the *New England Journal of Medicine,* perhaps the most prestigious medical journal in the world, was among the first to speak out strongly about the risks of conflict of interest and requiring the routine disclosure of the investigators' financial ties along with publication. This was an important first step. After all, if you want to critically evaluate a research article, it's reasonable to want to know if the investigator had a financial stake in the outcome. Sadly, while everybody seems to agree with Dr. Resnick in principle, not all journals have taken such a firm stand on the right of the reader to consider possible conflicts-of-interest just as carefully as a study's methodology. Happily, this seems to be an area the National Institutes of Health is showing leadership in at this time, and some of the federally-funded research groups are already drafting, or putting in place, much stronger conflict of interest disclosure policies.

HIV & Breast Feeding: What's a Mother to Do?

By Rebecca Denison
Reprinted from WORLD, October 2001
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What's the background?

Most babies born to HIV-positive mothers will not get HIV. But some will. A baby can get HIV from its mother:

- During pregnancy (before birth);
- During delivery (the most common way babies get infected);
- Through breast-feeding.

Breast-feeding can increase the risk of HIV transmission.

Prolonged breast-feeding increases the risk of a woman giving HIV to her baby by about 14 percent. Here are what two studies of babies born to HIV-positive women show:

- Nairobi, Kenya—At 24 months, 20 percent of formula-fed babies became infected with HIV, compared to 36 percent of breast fed babies.
- South Africa—HIV transmission was 12 percent higher in breast-fed babies than in formula-fed ones at 15 months.

Formula feeding also has risks.

There is no HIV in baby formula, but formula that is not given safely can make a baby very sick. Making formula with dirty water, or serving it in a bottle or cup that isn't totally clean, can expose the baby to dangerous bacteria. According to the World Health Organization (WHO), babies in developing countries who are fed on formula are up to six times more likely to die from diseases like diarrhea and respiratory infections than breast-fed babies are.

Mixed feeding (breast + formula) is most dangerous.

Mixed feeding is the most dangerous method, because formula feeding can irritate the lining of the baby's stomach, making it easier for the HIV in breast milk to get in and cause an infection. In a South African study of HIV-positive women and their babies, 36 percent of babies who received mixed feeding were reported infected compared to about 25 percent of those who were exclusively breast-fed and 19.5 percent of formula-fed babies.

What's an HIV-positive mother to do?

In the United States and other developed nations, HIV-positive women are advised to not breast-feed and to use formula instead. This is because most women in these regions have easy access to formula, clean water for mixing and washing, and refrigeration. Women in developed regions can usually get health care if the baby becomes sick to prevent a case of diarrhea from becoming fatal. While formula feeding may be the most obvious choice for preventing HIV transmission, it's still not easy to use.

During the first years of the epidemic, in developing countries where many people do not have access to clean water, HIV-positive women were often advised to breast feed their babies to protect them from the health problems related to formula feeding. Today, some people still feel that's the best advice, while others feel that women should have more information, more choices and better access to affordable formula. Whichever method a woman chooses, there are some things she can do to make it safer.

Breast feeding exclusively for 6 months or less is less risky.

Researchers agree exclusive breast-feeding (where no other foods or liquids are given) is safer than mixed feeding. However, they disagree about whether women will realistically be able to do so. A study from South Africa showed that after an educational campaign, 72 percent of participants were able to breast feed exclusively. However, a study in Uganda reported that, of 60 women who used breast-feeding, only six actually breast-fed exclusively. As more people learn about the benefits of exclusive breast-feeding, the number of women who do it will likely rise. But, as several Ugandan women at a recent conference said, it would still be hard for most women to do without exception.

The risk of a baby getting HIV from breast-feeding increases the longer the baby is exposed to HIV in the breast milk. When breast-feeding is stopped at six months, the risk of transmission is reduced—some say to as little as 5 percent (compared to 14 percent with longer periods of breast-feeding).

What about women who don't know their HIV status?

It is difficult for women to make informed choices when they do not know their HIV status. Some don't know because they are afraid to be tested. In many places, women don't have access to voluntary counseling and testing. Steps are needed to make testing available and to reduce discrimination against those who test positive.

It took years of public health campaigns to teach people that "breast is best." (Of course, if the mother is HIV-negative, breast-feeding is still the best choice.) When these campaigns began no one predicted the AIDS epidemic. Now some believe that every effort should be made to obtain free formula for those who want it—including changing laws enacted that prohibit formula makers from giving away free product as a marketing strategy. Others think breast-feeding should still be actively promoted for HIV-positive women, fearing that if women with HIV start using formula, there may be a "spill over effect" in which women who are not HIV-positive or don't know their status opt for formula too.

What about the mother's health?

Much of the breast-feeding debate has focused on the baby, however a study in Kenya suggested that women who breast-fed got sicker, faster than those who used formula. This may be because a breast-feeding woman needs the extra calories, nutrient and fluids for her own body's health.

What about HIV drugs?

HIV drugs can reduce the risk of a baby getting infected from breast milk by reducing the viral load in the mother and her milk and by improving the mother's health. However, HIV transmission can still occur through breast-feeding and, in the U.S., HIV-positive women on therapy are encouraged to formula feed. Most women in developing countries do not have access to HIV drugs. Some studies are looking at giving HIV drugs to the mother (or the baby) throughout the breast-feeding period to reduce the chances of HIV transmission to infants. Broader campaigns are working to make HIV drugs available to all HIV-positive people—adults, children and babies—worldwide.

More options and strategies:

Modifying cow's milk.

Cow's milk has too much protein and salt for a baby's kidneys to process, and not enough calories. However, full fat cow's milk can be modified. For example, for a 1–3 month old infant: mix 2 parts milk + 1 part clean water + sugar to taste, then boil. Whatever baby doesn't drink should be thrown out.

Heat treatment (pasteurization):

Breast milk should not be boiled, but it can be heat treated to inactivate the HIV in it by placing a jar of expressed milk in a pot of boiling water, removing the pot from the heat and leaving the jar in the pot for 60 minutes.

Another strategy is to leave expressed breast milk at room temperature. Unlike formula, which spoils after an hour, breast milk can be left out for several hours before it begins to go bad. Although leaving breast milk to stand won't eliminate the HIV, it may reduce the amount of virus in the milk.

Alternative breast milk sources.

It may be possible to have another woman breast feed the baby or to get breast milk from another woman or from a milk bank. However, this assumes that the woman has tested HIV-negative, is still negative, and that she will not become infected with HIV for as long as she is providing milk. Naturally, this is not an easy thing to guarantee.

For women in the U.S. and wealthier countries

Although HIV-infected women in the U.S. and other developed countries usually have access to clean water and formula The decision not to breastfeed is not always easy.

Breast-feeding is the norm in most developed countries, and women who bottle-feed may fear questions about why they don't use their breast milk. Birthing classes, WIC, and other programs directed at pregnant women and new mothers actively promote breast-feeding. Many HIV-positive women have had to lie or disclose their status to get counselors, teachers or social workers to stop pressuring them to breast-feed. Often these activities take place in a group, which can cause a woman to become concerned about her confidentiality being violated, or about feeling social isolation when everyone else is having a different experience.

An HIV-positive woman who breast-feeds and discloses that choice could possibly face a legal threat of having her children removed by authorities. Since most people who know of an HIV-positive woman's status believe she has made the safest choice for her child when she formula feeds, they may overlook giving her an opportunity to express her anger or sadness about not being able to breast feed her child.

What should the message be?

There has been great debate about what women who have HIV, or those who live in high-risk areas, should be told about HIV and breast-feeding. Some argue that HIV-positive women should be given all the information and be encouraged to make the best decision they can based on the realities of their own situations. Others worry that people are getting mixed messages and that the confusion is dangerous. People on all sides of the debate want to do what's best—but there are still disagreements on what that is.

Breast feeding Versus Formula: Risks and Benefits

Exclusive breast-feeding

Exclusive breast-feeding is giving the baby breast milk only.

Risks:

Breast-feeding increases the risk of a baby getting HIV by up to 14 percent. A baby will be at greater risk of getting HIV through breast feeding if the mother:

- Breast feeds her baby for a long time (this is why many suggest weaning by 6 months if the mother is HIV-positive);
- Gets infected with HIV while breast feeding;
- Gets cracked or bleeding nipples;
- Gets mastitis (a breast infection);
- Is very sick, or has a high viral load or a low CD4+ count, or has a lot of virus in her breast milk.

Breast-feeding is hard on a woman's body. To maintain her health and milk flow, she needs extra calories and fluids.

Benefits:

- Breast milk is very nutritious and helps protect a baby from diseases;
- Breast-feeding can help a mother and baby bond (although a formula-fed baby and mom can bond just as well);
- Breast-feeding may help a baby that is born infected stay healthy and avoid germs from formula feeding;
- A woman is less likely to get pregnant while exclusively breast feeding, helping her to space her children.

Replacement/formula feeding

Risks:

Some common problems related to formula feeding include:

- Infections from germs in water used to mix formula or spoiled formula can be extremely dangerous;
- Formula-fed babies miss out on the health benefits of colostrum and many of the nutrients in breast milk;
- People may wonder why a woman isn't breast feeding and ask if it is because she has HIV;
- Mixing too little formula (watered down) or too much formula can make a baby sick;
- It takes work to boil water and keep all utensils clean every time baby is fed;
- Formula is expensive. Paying for it means less money is available to pay for other basic needs;
- A woman who does not breast-feed will get periods and become fertile sooner. If she does not want to get pregnant right away, she'll need contraception immediately.

Benefits:

- There is no HIV in formula. A baby born HIV-negative can stay HIV-negative;
- Others can help feed the baby if the mother needs a rest, gets sick, or has to go away for work or other reasons.

Mixed breast-feeding

Giving the baby breast milk and other drinks, such as formula, glucose water, gripe water or traditional medicines, is called mixed feeding. Mixed feeding is very common; however it is much riskier than exclusive breast or formula feeding. When possible, an HIV-positive mother should try to pick one method and do only that.

Risks:

Giving foods, formula or drinks to your baby can damage the lining of the stomach and intestines, making it easier for HIV in breast milk to infect the baby.

If it is so risky, why is it so common?

In many places, mixed feeding is the social norm. Women who choose to formula feed sometimes breast feed due to social pressure, fear of relatives discovering their HIV status, or not having enough money for formula.

Women who choose to breast feed sometimes use formula because they get sick, they have to leave the baby with someone to go to work, or they can't produce enough breast milk to adequately nourish the baby.

WORLD: *Women Organized to Respond to Life-threatening Disease*, is a diverse community of women living with HIV/AIDS and their supporters. To subscribe to the newsletter, contact WORLD, 414 13th Street, 2nd Floor. Oakland, CA 94612. Phone: 510/986-0340. Fax: 510/986-0341. Web site: www.womenhiv.org.

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Opinion

You Don't Own Me

By Gregg Gonsalves

For the past several years, I have become increasingly worried about how patents could affect our response to the AIDS epidemic. Many of us are familiar with the international debates about patents on AIDS drugs and the fight to use cheaper, generic, equivalents in the developing world. However, my particular concern is about a kind of intellectual property that is more insidious: the patenting of human genes and other kinds of genetic material, particularly HIV itself.

Two years ago, Human Genome Sciences (HGS) of Maryland was granted a patent on the gene for CCR5, one of the cellular receptors that HIV uses to infect cells. HGS didn't discover this receptor's role in HIV infection; they simply sequenced large swaths of the human genome and claimed patents for everything they collected. They only found out that CCR5 was a lucky catch when William Paxton, Richard Koup, John Moore, Daniel Littman, Nathaniel Landau and other leading researchers did the hard work to pinpoint this protein's critical importance in AIDS.

The U.S. Patent and Trademark Office (USPTO) subsequently made it more difficult to patent genetic material without accompanying knowledge of a specific, substantial, and credible use for a given gene and its proteins. But over 6,000 gene patents had already been granted under the old criteria and at least 20,000 more were pending approval when the guidelines changed. Scientists trying to develop new drugs for HIV based on CCR5 or any other protected gene—human or retroviral—may have to negotiate a thicket of patents, perhaps paying licensing fees to more than one party. This could unduly hold up the development of novel therapeutics for HIV. As HGS CEO William Haseltine said in 2000, "If someone in a company wants to use the CCR5 cloned gene, they may need two licenses: our license for composition of matter and a license [from NIH research by Edward Berger] to practice HIV inhibition."

My concerns around the patent on CCR5 are theoretical as far as I know. However, there have been some real and devastating consequences from the patenting of HIV itself, in particular, the patent on HIV-2, owned by Bio-Rad Laboratories, Inc. Bio-Rad has refused to grant U.S. licensing rights for HIV-2 to several small companies with proven rapid diagnostic tests for HIV-1/HIV-2. These tests have revolutionized HIV testing outside of this country by providing reliable results within minutes. But the three companies with U.S. licenses from Bio-Rad, Abbott Laboratories, Johnson and Johnson and Chiron Corporation, either make their own rapid tests—though not for sale in the U.S.—or have no interest in developing these tests, perhaps because of lucrative franchises involving the more expensive, slower laboratory-based assays that dominate the market here in the 50 states.

Each year in the U.S. over 700,000 people come in for HIV testing but do not return for their test results according to the CDC. How many people have missed receiving an HIV diagnosis because of the intransigence of Bio-Rad and their secret licensing agreements that seem to be keeping rapid tests out of the U.S.? How many more HIV tests could be done with the resources saved by using these cheaper testing alternatives? The incidence of HIV infection in the African-American and Latino communities in the U.S., especially among young gay men, has skyrocketed over the past few years, with rates rivaling those of some countries in sub-Saharan Africa. Making HIV testing simpler and more accessible for hard-to-reach populations is a key part of improving our HIV prevention efforts in the communities hardest hit by the epidemic. Rapid tests would be an important new tool in our fight against HIV here in the U.S. According to Bio-Rad, they'll be submitting an application to the FDA sometime soon for approval of their own rapid test kit. I don't think we have the time to wait when there are dozens of different rapid tests already in use across the globe.