



Abracadabra: Magic Johnson and Anti-HIV Treatments

Part I—"Background"

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"It's not going to happen to me. And I'm here saying that it *can* happen to anybody, even me, Magic Johnson." These words were spoken by basketball hall-of-famer Earvin "Magic" Johnson at a press conference on November 7, 1991, to the shock of an entire nation. Johnson represents one of the first sports celebrities to publicly announce his HIV-seropositive status. A star basketball player who is HIV positive? How could this have happened?

In 1992, Magic played in the NBA All-Star Game and on the gold-medal-winning U.S. Olympic basketball team. He served as head coach of the Lakers in 1994 and returned as a player on the team in 1996, but decided it was time to retire and channel his energies into other arenas outside of basketball. Currently, Johnson is CEO of his own business, Magic Johnson Enterprises (MJE). He also has established the Magic Johnson Foundation, which helps inner-city communities deal with issues surrounding HIV/AIDS and raises funds for research and prevention efforts. His time is also spent with his wife and three children.

Johnson exercises regularly and eats a healthy diet. He currently does not experience any of the symptoms associated with HIV infection or AIDS.

Questions

1. What is the difference between HIV and AIDS?
2. List and explain the major routes of HIV transmission.
3. What does seropositive mean and how is a person tested for HIV?
4. What are some symptoms associated with acute phase HIV infection? What are the symptoms of AIDS?
5. What benefits are associated with Magic Johnson's announcement concerning his HIV-positive status? What risks or drawbacks can you think of associated with his announcement?

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Part II—"A Magic Bullet or Magic Medicine?"

by

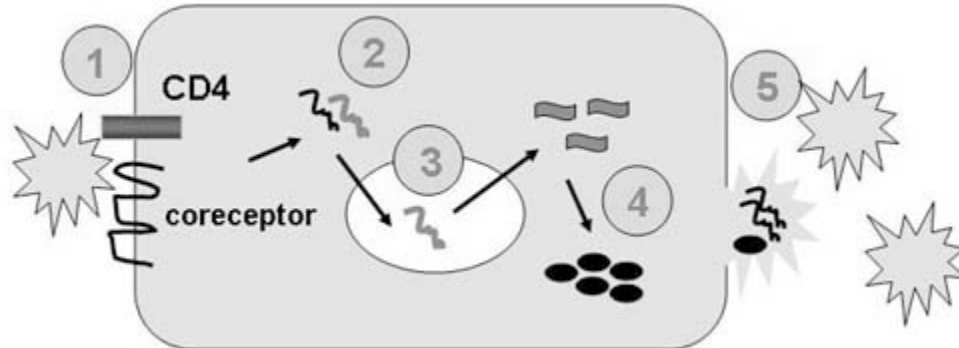
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Although Magic Johnson tested positive for HIV in 1991, his routine HIV tests show that his virus load is currently at undetectable levels and does not show AIDS-related symptoms. Thus, Johnson is considered a non-progressor. Many people who are non-progressors live with HIV without major health complications and their immune system seems to keep the virus under control. Progressors are people who have uncontrollably high virus load levels and advance to AIDS quickly, usually within five years after infection.

What keeps Magic Johnson alive and symptom free? In order to answer this, it's important to understand the several steps that occur during the life cycle of HIV.

HIV Life Cycle:



(1) Entry: HIV uses a receptor on its surface called gp160 (glycoprotein 160, aka envelope protein) to bind to T cells. The receptors on T cells that gp160 interacts with are CD4 and one of two chemokine co-receptors, CXCR4 or CCR5. Once bound to the cell surface, a conformational change in the receptors allows the virus to enter the cell.

(2) Enzyme 1—Reverse Transcriptase (RT): Once the HIV is in the host cell, the virus protective covering (nucleocapsid) degrades and releases the 2 RNA strands that comprise the HIV genome. The HIV genome is converted from RNA to dsDNA by the enzymatic action of Reverse Transcriptase (RT).

(3) Enzyme 2—Integrase (IN): The copy of the HIV genome in DNA form is inserted into the host's genome by the enzymatic action of integrase. Once inserted into the host genome, HIV is called a provirus. The HIV genome, which encodes for HIV proteins, is translated by host cell machinery into immature or nascent polypeptides that have no

function until cleaved into smaller polypeptides. Where in the host genome would be ideal places for the provirus to be inserted?

(4) Enzyme 3—Protease (PR): The nascent polypeptides are cleaved into mature, functional HIV proteins by the enzymatic actions of protease.

(5) Exit: Once the newly synthesized HIV proteins are synthesized in the host cell, the HIV virions assemble with all the necessary components and bud out of the host cell to produce new virus particles. The virion acquires the envelope proteins gp41 and gp120 as they bud. Hundreds or thousands of virions may be produced within a single cell.

Magic Johnson has worked with Dr. Michael Mellman, his personal physician for the past 20 years, to try to keep the virus under control using a combination of antiretroviral drugs. This combination therapy is termed HAART or Highly Active Anti-Retroviral Therapy. The "drug cocktails" that make up a HAART regimen combine the power of multiple drugs to block multiple targets in the HIV life cycle. Central to Magic's therapy regimen is a drug called Combivir®, a combination of two drugs: lamivudine and zidovudine, which are nucleoside reverse transcriptase inhibitors. You may be familiar with zidovudine by another name, AZT. HAART regimens can cost an average of \$1,000 per month or more depending on the source and type of drugs administered.

Johnson was recently hired as a spokesperson for GlaxoSmithKline, the company that produces Combivir®. The medication Magic Johnson takes is not a top secret magic bullet but rather a commercially available antiretroviral treatment. Thus, the same medication that Magic Johnson takes to control his HIV infection is available to everyone who is HIV-positive.

Questions

1. What is meant by virus load? Draw a graph of a typical virus load profile for an HIV-infected individual.
2. Based on the HIV life cycle, propose potential anti-HIV treatment targets. Which targets would be most effective in blocking HIV infection? Which targets would be least effective?
3. Propose biological and immunological reasons for why Magic Johnson's viral load levels are undetectable. Graph your ideas as a function of time, beginning with his initial infection through the present day. Since Magic Johnson's virus load is undetectable, is he cured of HIV? Support your answer with biological reasons.
4. What is the advantage of using multiple targets during HAART?
5. Do you agree with the statement "The drugs he takes are available to everyone"? What are some factors that might make this an overstatement?
6. As a spokesperson for GlaxoSmithKline, what impact will Magic Johnson have on how HIV-positive people are viewed? What influence will he have on the future of GlaxoSmithKline? On other HIV-positive African-Americans? What ethical aspects can you think of associated with using Johnson as a spokesperson by a pharmaceutical company such as GlaxoSmithKline?

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Part III—"Drug Treatment and Drug Resistance: A Double Edged Sword"

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The good news is that HAART has successfully treated HIV-positive patients, giving them extended lifespans, allowing the immune system to regain control, and decreasing virus loads. The bad news is that HIV is a smart virus; HIV has developed mechanisms to overcome the blocks imposed by drug treatments.

Through a microevolutionary process, HIV variants that are resistant to the intended inhibition are able to replicate and produce more virus. Over time, in the presence of a drug such as AZT, random mutations may develop and be selected for that allow these variants to be resistant to the effects of AZT. These drug resistant variants have greater fitness and can replicate in a person even in the presence of a drug. Specifically, mutations in reverse transcriptase (RT) develop in the presence of AZT. These variants allow HIV to continue to replicate in human T cells. HIV variants may only contain a single amino acid change in the protein sequence to render an anti-HIV drug ineffective.

For many years, doctors emphasized the necessity for strict compliance with prescribed HAART treatment regimens. Recently, a controversial new therapy called structured treatment interruption (STI) has been suggested to HIV-positive patients by their physicians. STI refers to the practice of alternating time spent on antiretroviral drugs with time spent off drugs, and each cycle may last anywhere from several days to months. However, it is not recommended for all HIV-positive patients. The theory behind STI is that the alternating periods of HAART treatment with regulated withdrawals of drug therapy may serve as a means of inducing immune system control of HIV.

Questions

1. How are natural selection and microevolution illustrated in this scenario? Identify the genetic basis for HIV evolutionary change, the selective pressure, and the resulting adaptation. What happens to mutants that are able to escape detection by the immune system?
2. Describe how mutations could lead to drug resistance in the RT enzyme. Include physical, molecular, and biochemical reasons.
3. Define compliance. Draw a curve of what the virus load profile would look like if a patient is not compliant. Label the X-axis with time and the Y-axis with virus load.
4. Why is STI considered a scientifically controversial strategy? Suggest *three* biological reasons why STI could be advantageous. Predict what will happen to the virus over time if patients are then allowed to resume their HAART therapy after STI. Propose situations in which the STI approach may not be recommended or effective in some HIV-positive people. How would a physician be able to tell if STI is working?

5. Predict what will happen to infection rates over time if drug resistant forms of HIV are allowed to spread through the population. What conditions might slow the spread of drug resistant strains?

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