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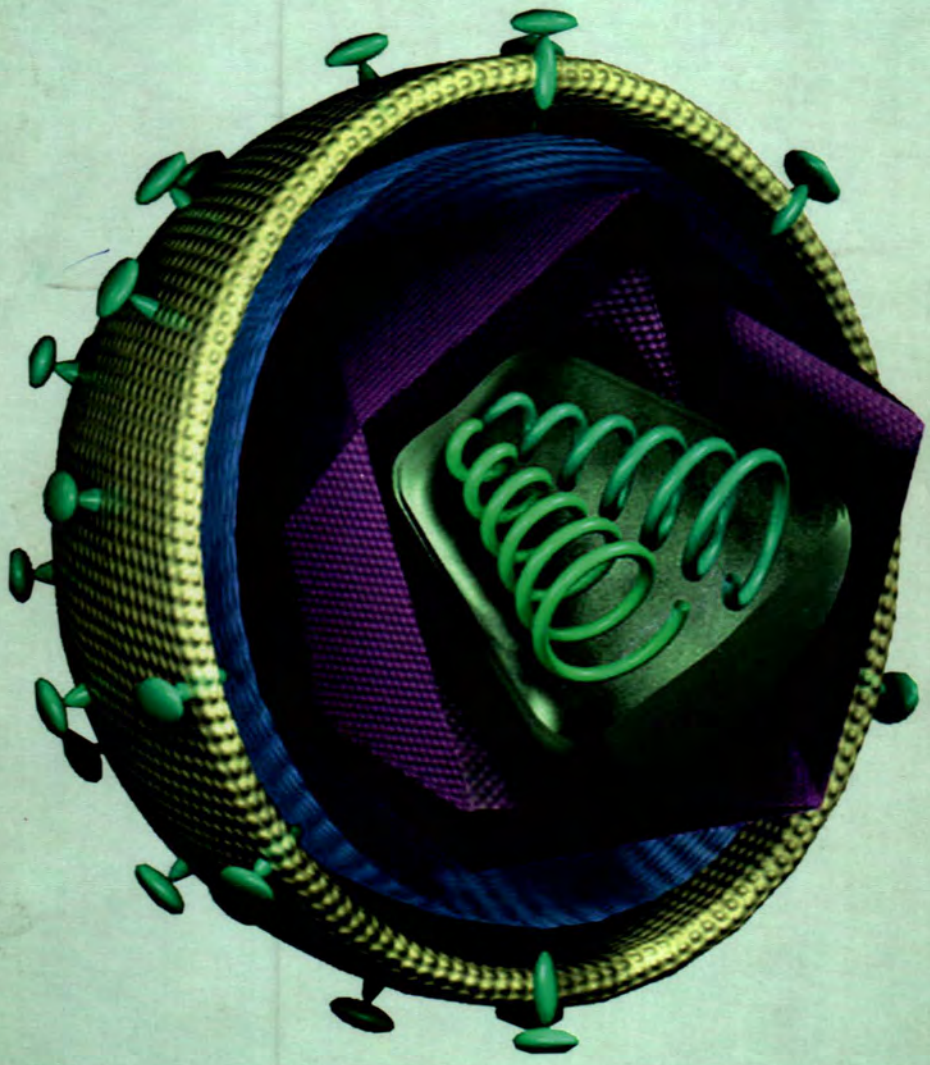

HIV/AIDS

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THE NEXT ISSUE

SPORTS MEDICINE

SUBMISSION DEADLINE
APRIL 5, 1998

SUMMER1998

SUBMISSION DEADLINE
NOVEMBER, 1998

www.med.uwo.ca/medjrnl/

COVER ART:

Computer generated structural model of a typical virus in the taxonomic family *Retroviridae*. HIV-1, the virus which causes AIDS, belongs to the Lentivirus group. The lentiviruses are exogenous, nononcogenic retroviruses causing persistent (chronic active) infections leading to diseases with long incubation periods. These viruses usually infect cells of the immune system (macrophages, T-cells) and cause cytopathic effects in permissive cells, such as syncytia, and cell death. Lentiviral infections are not cleared by the immune system, leading to accumulated damage over a period of many years. This important characteristic is reflected in the name of the subfamily (lenti- for slow).

The virion is pleomorphic in shape, spheroidal, enveloped, and 80-100nm in diameter. Small surface projections give the envelope a rough appearance; spikes are dispersed evenly over the surface.

The genome is linear, single stranded, RNA. The total genome of one monomer is 9200 nucleotides long.

Special Thanks to David Mai of Meds 98 for his artistic contribution.

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The UWO Medical Journal is an interdisciplinary medical publication, established in 1930. The Journal is published twice each academic year: Fall and Spring.

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NATURE OF THE JOURNAL

The purpose of the UWO Medical Journal is to provide a single forum for original articles based on research or clinical medicine of topical or historical interest. Since readership of the Journal is interdisciplinary, articles published will attempt to reflect a wide range of medical interests. In this regard, submissions should be directed towards the general medical reader. Articles which do not pertain to the feature topic will be given lower priority as will those with excessive technical jargon. Please restrict submissions to under 2,000 words.

Informal peer review is required, i.e., non-specialist authors are encouraged to collaborate with, or at minimum, have their work reviewed for content by a specialist in the field. This individual, if not a co-author, is to be acknowledged at the end of the paper. In addition, it is recommended that all submissions be proof read for significant stylistic or grammatical errors. The editor will not assume responsibility for corrections of this nature and articles requiring such revisions will be returned to the author.

Submissions and disks become the property of the Journal. The Journal reserves the right to correct errors of punctuation or spelling. Affiliation with UWO is not a prerequisite for authorship.

References are indicated numerically in the text[1] and listed as endnotes in order of appearance.[2] Do not use the 'endnote' feature of your word processing program; list references as part of the text on a separate page immediately following the body of the document. Punctuation comes before reference numbers and sentences are separated by one space only. Examples of Journal reference format follow below:

1. Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992; 339(2):347-50.

2. Dement WC, Carskadon MA, Richardson G. Excessive daytime sleepiness in the sleep apnea syndrome. In: Guilleminault C, Dement WC, eds. Sleep Apnea Syndromes. New York: Alan R Liss, 1978:23-46.

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Please direct submissions, including return address, phone and fax numbers, to: UWO Medical Journal, Health Sciences Building, Room MS-175, University of Western Ontario, London, Ontario, N6A 5C1.

Submissions are to include a cover letter, two double-spaced paper copies, and the full text on a 3.5" IBM compatible floppy diskette in Microsoft Word or WordPerfect format. The cover letter should be signed by all authors and indicate that the manuscript has not been published previously.

Short biographical notes on the authors are to be included at the beginning of each paper, on a separate page.

Figures should be professionally drawn; photocopying of illustrations from texts, without the permission of the publisher, is copyright infringement. Each figure, table, or illustration should be submitted on a separate page. Any illustration with a grey-scale should be in the form of a photograph. Two copies of each figure, table, or illustration should be included; each should have its number written on the back, as well as the name of the first author. Legends, which are to be included at the end of the text, should start on a separate page with Arabic numerals corresponding to the figures and tables.

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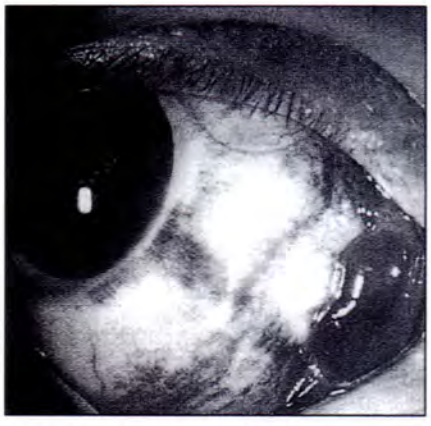
Articles and letters to the Editor may be submitted via our e-mail link on our site on the world wide web at our URL: www.med.uwo.ca/medjrnl/. Any documents intended for publication should be sent as attached files, and not as e-mail messages. Acceptable formats for attached files are document files of any version of Microsoft Word, or WordPerfect; other file formats will not be accepted. All elements of the submission, including biographical notes on the authors, body of the article, captions for tables and figures, and references should be included as described above. A statement indicating that the manuscript is original and has not been published previously should be included as a separate page at the beginning of the document file. Illustrations and photographs cannot be submitted electronically at present, and must be delivered or mailed to the Journal office.

Submit To Us!!

Interview with Dr. Michael J. Rieder, Recipient of the 1997 Douglas Bocking Award (P.25)

A Glimpse of the Face of AIDS in Tanzania (P.48)



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ABOUT THE EDITORIAL BOARD

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Jordan B. Solmon is a fourth year medical student with a Bachelor of Science degree from the University of Toronto. He will be pursuing residency training in General Surgery at the University of Toronto.

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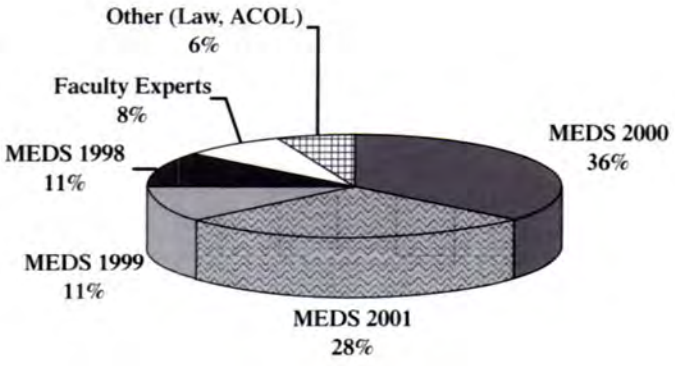
Daniel Hackam is a second year medical student at UWO.

The Medical Journal has undergone some major restructuring in the last year. This year, we have established regular departments, and staffed each with a Departmental Editor. We hope that these recurring sections will broaden the scope of the Journal and keep things interesting. An enthusiastic staff of 14 has settled into our new office, located in MS-175, Medical Sciences Building, and we have undertaken a campaign to increase both the visibility and the quality if the Journal. We have launched a new web site which can be visited at www.med.uwo.ca/medjrnl/ . For this issue, we received more than four times the average number of submissions that we typically get, and all of them were focused on our Feature Topic. We hope this marks the beginning of a new 'era', in which the Journal is eagerly anticipated, and the content is as informative and timely as it is diverse and interesting.

Jordan B. Solmon
Editor-In Chief
Meds 1998

CONTRIBUTORS TO THE FALL 1997 ISSUE



In the past, the Journal has had a subscription fee of $17.00. For several years now, this fee has not been collected, and there are not any plans to re-institute the fee. In lieu of this expense, we invite anyone who is interested, to make a charitable donation to the John Gordon Home. This is a hospice and supportive living facility for those afflicted with HIV/AIDS. All cheques should be made payable to the John Gordon Home, and sent to the University of Western Ontario Medical Journal office. Receipts will be provided. Thank you for your support of this worthwhile community resource.

EDITORIALS

HIV/AIDS and Cultural Evolution

Friedrich Nietzche professed that illness was vital for cultural development. When one evaluates the history of catastrophic afflictions which have beset humankind, the veracity of this notion is obvious. The Greeks had blindness, Medieval Europeans had the Bubonic Plague, and 19th century Europe had tuberculosis.[1] Presently, the truism is manifest as the scourge of HIV/AIDS. Culture is an inclusive term which encompasses a society's art, science, spirituality, commerce, and patterns of interaction; it denotes a group's Worldview. In the Western world, every facet of the population has been given voice by the AIDS pandemic.

Explanations for the origins of HIV are numerous. Theories range from accidents in U.S. and Soviet laboratories involved in biological warfare, to green monkeys that harbored the disease and propagated it to Man in Africa[2], to Patient Zero, allegedly a promiscuous Canadian male homosexual airline steward, who recklessly spread his own rare illness.

Demagogues, in some cases, revel in self-satisfied assuredness as their preaching seems validated: just as the biblical cities of Sodom and Gomorrah were destroyed for licentious behavior, Cardinal Ratzinger of the Roman Catholic church cited HIV/AIDS as God's wrath against a permissive society and the abomination of homosexuality.[2]

The artistic community has exploited its pulpit in the media, and has been a visible, if not venerable philanthropic force. The AIDS Awareness Ribbon was inspired by the yellow ribbons worn on jacket lapels, during the Persian Gulf War, to honour American soldiers. Conceived by Visual AIDS, a New York based charity group of professional artists, they chose the colour red because of its connection to blood, and its symbolic association with emotions such as anger and passion.[3,4] Worn by host Jeremy Irons at the 1991 Tony Awards, the AIDS Ribbon made its public debut.

A militant faction of skeptics exists, and alleges that in 14 years, the "HIV hypothesis" has been unproductive, and non-predictive, due to the fact that AIDS is neither an infectious epidemic, nor is it caused by HIV.[5] Activist groups, such as Continuum, seem to be belligerent in their denial of the HIV/AIDS crisis. Expounding their premise that HIV does not exist as a unique exogenous lentivirus, they argue that the global promotion of anti-viral drugs is responsible for the spread of AIDS-like symptoms. They have crafted a hypothesis which states that the condition is the iatrogenic consequence of a despotic medical and pharmaceutical conspiracy.

Championing the war against HIV/AIDS, medical professionals and community based agencies have indeed experienced their share of triumphs and disappointments. Retroviruses were first postulated, and then discovered, in the early 1970's.[6] By 1982, HTLV-1, the first human retrovirus had been isolated and characterized.[5] In 1980, the first scientific report on the subject was published. It concerned homosexual males, from the Los Angeles area, who had presented with unusual skin infections and cancers.[2] An early bias, which is perpetuated even today by ignorance and hatred, was established in 1981: based solely on the demographics of the earliest, isolated cases, the disease was named Gay Compromise Syndrome.[7] This term, with its negative connotations, was eventually replaced by the acronym AIDS. The virus responsible for AIDS was isolated in 1983 by researchers at the Pasteur Institute in France, and they called it Lymphadenopathy-associated Virus (LAV). The International Committee on the Taxonomy of Viruses recommended the use of the term Human Immunodeficiency Virus (HIV) in 1986.[2]

1997 has been deemed a pivotal year in the ongoing battle against HIV/AIDS. Combination therapies, known as "drug cocktails " are widely prescribed, and declines in the rate of death from AIDS in developed countries have been reported. Plasma HIV-1 RNA determinants have

usurped CD4 cell counts as the most important marker of HIV progression and prognosis. Nonetheless, a daunting reality remains. It is stated in a recent commentary in the CMAJ that drug resistance and inaccessibility of therapeutic agents, as well as a resurgence of new infections in key populations, pose continuing challenges.[8] Community health units and educators fear that an attitude of complacency has resurfaced amidst the optimism of promising recent developments.

Services available to those whose lives have been affected by HIV/AIDS are as diverse as the patient population itself. From the throes of suffering has emerged a climate of medical urgency and social awareness and tolerance.

The University of Western Ontario Medical Journal has devoted this issue to the topic of HIV/AIDS because it is relevant to medical practitioners at all levels, and in all fields. We hope that this issue will serve to educate our readers, and to supplement the information regarding HIV/AIDS that is currently presented in the medical curriculum at Western. Ω

Jordan B. Solmon
Editor-In-Chief
MEDS 1998

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ETHICS

EDITOR: DAVID SATIN

A Practical Method for Approaching Bioethical Issues

By Fady Balaa and Asif Doja, MEDS 2000

Individuals entering the field of medicine come from varied and diverse backgrounds; as a result, some people have had little or no experience in the study of biomedical ethics, whereas others have multiple degrees in the field. Nonetheless, every medical student will come to a point in his training where he will encounter a situation that will demand ethical analysis. More to the point, he will be forced to make decisions that he will have to justify to his supervisors, colleagues and patients. The purpose of this article is to introduce a practical method of analysis that students can adopt and improve upon as their careers progress.

Presented here is an approach for examining ethical dilemmas which was developed by Dr. Keith Arnold from the Department of Philosophy at the University of Ottawa. This approach is a very practical one for medical students since it is straight forward, case-specific, and allows for all aspects and viewpoints of a particular issue to be presented. This is neither the only method for examining moral problems, nor is it necessarily the best -- it is simply one particular procedure which students can use, modify or even discard, as they deem appropriate.

INTRODUCTION

Before methods for examining ethical issues can be discussed, it is important to formulate agreed upon definitions of certain terms. The most important of these concepts would have to be that of an ethical dilemma. An ethical dilemma can be seen as a conflict which arises when two or more parties disagree; to do good for one party may be to do harm to another. Essentially, it is a situation wherein one is not simultaneously able to satisfy everyone's wants, needs and rights. From this definition, it follows that a blanket term such as "abortion" does not in itself constitute an ethical dilemma. Instead, this concept has to be applied to a specific situation. For example, we could have a situation in which a couple disagrees, as the woman desires an abortion and the male wishes to prevent the abortion (i.e. the 1989 Jean-Guy Trembley v. Chantal Daigle case). Essentially, the example demonstrates that an ethical dilemma by definition arises only when we have two opposing viewpoints.

ABOUT THE AUTHORS

Fady Balaa and Asif Doja both completed their undergraduate degrees at the University of Ottawa and are presently in their second year of Medicine at the University of Western Ontario.

PRINCIPALISM VS. PROCEDURALISM

In the field of Biomedical ethics, there are two general approaches for examining moral problems. Principalism, or 'the engineering model', involves applying a set of rigid principles to a case. Proceduralism involves the evaluation of each case based upon the specific data presented. It is this latter approach that will be focussed on.

Principalism is also called the 'top-down approach' as it implies that the process of ethical problem solving is deductive, rather than inductive. The principles used are insensitive to the facts of different cases, and there is an implied certainty to the answer that results. The four principles are:

1. Principle of Respect for Persons (Autonomy): states that one should respect all those involved in a dilemma as persons, with dignity, freedom and the capacity for self-determination. A person should never be used as a means to an end.
2. Principle of Non-maleficence: one should attempt to inflict no harm. If one cannot do good without doing harm, then one should forego that course of action.
3. Principle of Beneficence: one should attempt to maximize benefits and decrease harm.
4. Principle of Justice: one should treat equals equally and unequals unequally. The goal is to appreciate the difference between the encumbered and the unencumbered. For example, it is obvious that a person in a wheelchair differs in some respects from an able-bodied person, thus in the spirit of leveling the playing field, the individual in the wheelchair may be entitled to certain privileges the able-bodied person does not have.

Recently, there has been a shift away from Principalism to Proceduralism, or the 'data driven method'. This method of ethical analysis involves the examination of each dilemma on a case by case basis. In this approach, there are no set standards with which to evaluate a case. Instead, each case is seen as unique, and we see a bottom-up methodology. The reasoning involved is inductive. It is vital to acknowledge the many points of view of all those involved in order to appreciate the perspectives from which the case can be viewed. To this end, the procedural approach uses strategies for examining different viewpoints. The goal is to utilize the different strategies and then to see if one still arrives at the same conclusion. An advantage of the specific procedural approach presented here is that one's own personal beliefs are incorporated, as are the aforementioned principles, as well as pertinent laws, codes and medical facts.

THE PROCEDURAL APPROACH

I. CASE SPECIFICATIONS

This initial step is perhaps the most crucial link in the chain of steps implemented in the procedural approach. The center of the entire procedural approach stems from the consideration of the specifics of each case. By developing a micro-history of the case, the uniqueness of situation is recognized.

II. IDENTIFY STAKEHOLDERS

Ethical dilemmas encountered in the health care profession are often not limited to one or two individuals, but instead involve a multitude of people who will eventually be influenced by the issue. As such, a stakeholder is defined as any individual who has an interest in, and will be affected by, the decision being made. There are three kinds of stakeholders:

First Party: The individual who is directly affected by the decision being made. Most often the patient is the primary stakeholder.

Second Party: Any individual who is involved in the decision making process, which will ultimately influence the first party. This includes the physician, and nurses.

Third Party: Any other individual who is indirectly affected by the decision being made. This includes family, friends, and others.

III. IDENTIFY MORAL DILEMMA

Any attempt to reach common ground in such situations requires that all parties involved recognize the same basic ethical dilemma. The following is an example of a specific ethical dilemma: A physician's right to breach patient confidentiality in order to protect the health of other individuals vs. a patient's wish that confidentiality be upheld at all costs.

IV. IDENTIFY COMMUNITY STANDARDS

Society and the perspective of the community at large will tend to influence the outcome of an ethical dilemma. The opinion of the community at large can follow one of two patterns:

1. Null Hypothesis: The community at large is in agreement regarding the issue, and thus the greater percentage of people lie on one side of the argument.
2. Moral Equipoise: The community is divided equally in terms of percentage for and against a specific argument. As such, no community standard exists.

V. CONSIDER PERSONAL VALUES

At this stage of the ethical analysis, it is suggested that one should introduce his own personal values and beliefs. These personal opinions are not meant to be the ultimate factor in reaching a decision, but instead play a role of guidance. By doing this, the examiner brings himself closer to the case and thus ensures that the final decision reached will be as humanistic as possible.

VI. CONSIDER PERSPECTIVES OF STAKEHOLDERS

The perspective of all the stakeholders who will be influenced by the decision being reached must play a role in the decision making process. This is yet another link, in the chain, which emphasizes and allows for the recognition of the uniqueness of each case. Certainly, identical ethical dilemmas will appear time and time again, however the individuals involved in the dilemma will differ from situation to situation. As such, this step will ensure that the needs, rights, and wants of any individual are not overlooked due to generalizations which might stem from previous experiences.

VII. EXAMINE CASE INDEPENDENT VARIABLES

Despite the emphasis placed on examining the uniqueness of each situation, there are stages when the examiner must consider factors that are consistent from case to case. It is important to recognize that these parameters should not play the role of an ultimate authority in the decision, but instead should offer some guidance in the decision making process. The following are some example of case-independent variables:

1. The four pillars of the procedural approach: Principles of autonomy, non-maleficence, beneficence, and justice (discussed earlier)
2. Codes of ethics: There are various codes that are expected to regulate the conduct of physicians, nurses, and other members of the health care team, and thus offer protection to those who will be influenced by the decision. These codes include the Canadian Charter of Rights and Freedoms, Ontario Human Rights Act, Canada Health Act, and Canadian Medical Association Code of Ethics.
3. Pertinent laws: The Criminal Code of Canada, and several other bills provide guidance to physicians and health care workers when making decisions regarding ethical dilemmas. Nonetheless, there are continually new situations arising which the law has not been exposed to, and thus can not regulate.
4. Medical facts: The medical background of the case being considered, and the success rates of the various options should be considered.

VIII. APPLY PROCEDURAL STRATEGIES

The procedural approach offers strategies that the examiner can apply in order to facilitate the case analysis. This stage is particularly useful, because it ensures that experiences from previous cases are not transferred into the analysis. The four strategies are:

1. Role/Reversal: The examiner considers the situation as if he was in place of the first party. As such he will ensure that none of the actions taken will treat the first party unfairly.
2. Hard/New cases: The examiner changes the case to make it more difficult. In this instance the examiner considers the viewpoints of family members and other stakeholders, by placing people who are close to him in the position of the first party. Analysis of this new and more complicated case facilitates the analysis of the original one.
3. Maxi-Mini/Mini-Max: The examiner should follow a course of action which will maximize the benefits and minimize the harms. The worse outcome should be avoided at all costs.
4. Universal consequences: The examiner should consider the consequences if all other identical cases were handled in the same manner. What would happen if all others did what he is about to do?

IX. COME TO A DECISION

The end result of every ethical dilemma is that a decision has to made. After all the information has been gathered and the perspective of all those involved has been considered, the examiner can reach a conclusion regarding the best possible plan of action. In doing so the examiner will consider the arguments for and against each side of the dilemma. It is important to note that certain arguments will be more influential than others. Regardless of the conclusion reached, the examiner must strive to ensure that the final outcome is fair (or at least is not unfair) to all the stakeholders.

The control over life and death associated with the medical profession, today more than ever, implies that future physicians can expect to repeatedly encounter new and unanticipated ethical dilemmas, many of which will have no laws or precedents to refer to for guidance. It is hoped that the material presented here will be of use to medical students in formulating their own strategies to deal with ethical issues.

Ω

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1. *This report is based on a series of lectures present by Dr. Keith Arnold in the course Bio-Ethics PHI 2396 offered by the department of philosophy at the University of Ottawa, Sept. –Dec. 95'.*

DOCTOR'S CALL

By Dr. Jeff Nisker, LHSC-UC

The set is a mirror image framed by two small tables holding telephones with answering machines. Within the tables' boundaries stand Toni, stage right, and Tony, stage left. Toni is a 40 year old woman in moderate make up, business suit (reasonably casual) over a light sweater. Tony is a 40 year old man wearing sport jacket, open shirt and casual trousers. They stand back to back in freeze, centre stage. They then take one step lateral and one forward, and freeze. After 5 seconds tandem monologue begins.

TONI & TONY (in unison): My parents christened me

TONI: Antoinette

TONY: Anthony

TONI & TONY (in unison): My friends call me Toni(y).

TONI: I came home from the ritual post-work physical ablution that grants my home serenity.

TONY: My answering machine glance (they indicate respective answering machines) was met by the usual red staccato response.

TONI: This message lay waiting one hour ago.

DOCTOR'S VOICE (tape reveals a fatigued, worried female voice): Hi Toni(y), it's Norma Evans. Could you please call me when you get home . . . um . . . It's kind of important . . . sigh . . . please call me. (click, tone)

TONI (points to answering machine): My family doctor, Norma Evans, requesting return of her call . . . tonight . . . in such despairing voice.

TONY: The despair in her voice chilled me... Norma is one of the most upbeat people I know. (brightens) We went to medical school together.

TONI: Everyone responds upbeat to my tape's effervescent a capella invitation. Though more my trusted doctor than friend, Norma usually responds in matching accent and musical motif. (countenance darkens; gazes ahead sadly).

ABOUT THE AUTHOR

Jeff Nisker is a Professor of Obstetrics and Gynaecology at the University of Western Ontario and Coordinatore of the Yellow Brick Road Narrative Bioethics Programme. "Doctor's Call" was performed in 1997 for AIDS Vancouver during AIDS Awareness Week, and has also been performed this fall for the Canadian Bioethics Society and Dartmouth University.

TONI & TONY (in unison): But not tonight.

TONY (serious): Her tone bore hollowness to my core. You see a few days ago I went to Norma's office (pause) for an HIV test.

TONI: As my relationship with Bob was stable, (pensively) what am I saying stable? I'm sure he's the soulmate I've sought... for so many years, and since I started the pill four months ago, I felt it was time we could "de-condomize" our relationship. I know Bob wants to "de-condomize", really wants to "de-condomize". Even though I was not "at risk" for HIV, responsibility dictated I first have an HIV test.

TONY: I was to see Susan on the weekend and obviously wanted the all-clear as soon as possible.

TONI: But Norma explained that though the blood is couriered to the lab, it usually takes two weeks before the results are mail-returned.

TONY: Considering our mail system, I resigned to three weeks; but the fact that Norma was calling me in just three days... in such sadness... must mean that she was called by the public health lab to contact the HIV "carrier" (pause, points to self) immediately to ensure no further spread of the virus.

TONI: As I replayed the tape, my doctor's voice inflected no chromatic quality to contrary convince.

TONY: My immediate phone to my physician's home heard babysitter words apologize "Dr. Evans is working late in her office; she'll be home in about an hour."

TONI: Controlled fingers purposefully pressed each offered number... only to receive a receptionist's cheery taped message, (mimic) "I'm sorry, the doctor's office is closed and will reopen at 9:00 a.m. tomorrow. In case of emergency page the doctor on call." (pause) Before my whispered "please may my doctor be on call", her associate's name pierced my prayer.

TONY: I could not reach my doctor to certify my sentence.

TONI: To commute my condemnation.

TONY: The babysitter's approximation of Norma's ETA to confirm my already accepted sentence, afforded an hour to reflect my source of HIV and how to tell my loved ones.

TONI: *I've been in two prior relationships. Oral contraceptives protected me from pregnancy, but obviously not from HIV. At that time, I perceived no need for condom precaution. I'm sure my partners were strictly heterosexual. And I don't think they were unfaithful to me.*

TONY: *My previous partner is also a physician. I don't think she ever submitted for an HIV test. Could she have picked up HIV in the office, the ER? I know that's impossible . . . what am I saying (can't believe self; shaking head)--I'm a physician!*

TONI: *I know you need a significant inoculation of the virus, more than you can get from looking down a patient's throat or being coughed upon. Oh my god, I can't believe what I'm saying! I'm a physician!*

TONY: *I'm sounding like the fearful uninformed, afraid to come close to, or administer care to, people with HIV. I'm a physician... I should be enlightened... I should be sympathetic.*

TONI: *Was my previous partner always faithful to me? I never questioned his faithfulness before. But there were times, especially toward the end of our relationship, when things were quite bad between us. I didn't even want to be near him. I'm sure he knew it.*

TONY: *Until this minute, I never perceived my previous partner could have been unfaithful. My Pollyanna ethos assumes everyone as loyal as I... but the possibility exists. I never felt with anyone the emotional unity sewn so completely with Susan. I didn't know it could exist until Susan. Perhaps my former partner felt my disconnection and sought intimacy elsewhere.*

TONI: *Could Jim have picked up HIV from some woman and passed it to me? Some woman who gave him the comfort I couldn't. Woman?... Oh... Could it have been a man? Could Jim be bisexual? I don't think so. But how would I know?*

TONY: *How could I be so stupid? To succumb my sons to their father's slide through Hell, to being fatherless at the age they need me the most. (pause) I broke faith with my sons when I trusted the faithfulness of others.*

TONI: *How could I be tempted by trust?*

TONY: *I can't believe I hear my voice condemning others for what is clearly my responsibility. Have I descended to seek share of responsibility? It's my fault for my misfortune, full stop! Not misfortune... foolishness.*

TONI: *There was a patient during whose surgery a large-gauge needle went through my glove, (looking at fingers) far into my finger's flesh.*

TONY: *I clearly remember my run to employee health right after surgery for blood tests, to see if I needed a hepatitis shot. I had not thought about that man in years.*

TONI: *But I remember his face so clearly now. I see his eyes when, just as he was ready to leave hospital, I asked him to be tested for HIV.*

TONY: *I really did ask him. Physically holding back coercive consonants in the name of respect for his freedom to choose, to choose whether or not to be tested.*

TONI: *But I did compassionately encourage him to be tested.*

TONY: *I remember how relieved I was when he consented to the HIV test.*

TONI: *Although his HIV test was negative then, he could still have had HIV. What if he picked it up within the previous 6 months? His blood may not yet have converted to HIV positive.*

TONY: *If he eventually became HIV positive, you would think that he would have called the hospital to warn us, but how would he know unless he was re-tested? Or developed symptoms of AIDS?*

TONI: *Symptoms could take years to surface.*

TONY: *But he wasn't gay. At least, I don't think he was gay. But that's not something we asked about in those days.*

TONI: *And though sexual orientation is part of one's social history, I'm not sure we ask about it today.*

TONY: *I'm not sure we should ask about it today.*

TONI: *Will I ask my patients about sexual orientation from now on? (freaking) What am I talking about? There is no "from now on"! What patient in their right mind would want me for their doctor?*

TONY: *Will I have to inform each patient of my HIV status before I accept them into my practice (pause) or touch them? Is that what those doctors with HIV do?*

TONI: *(exacerbated) Is it fair to ask a patient to remain in my care or consent to physical exam?*

TONY: *Some may say yes to please me, but I know how great is the fear of AIDS. I feared it myself.*

TONI: *(exhausted) I see myself leperized: patients not shaking hands, making sure I don't come too close, backing out of my examining room.*

TONY: I see them looking for a sink

TONI: To wash their hands,

TONY: To cleanse each pore of possibility,

TONI: Before they get in their cars,

TONY: Carry contagion (pause)

TONI: To their partners (pause)

TONY: To their kids.

TONI & TONY (in unison): Do I change my practice?

TONI: Restrict my care to others same virus infected?

TONY: Rather than worrying my patients?

TONI: Rather than worrying about my patients? (pause)

TONY: When I asked my doctor for an HIV test, she asked if I wanted to "number-code-conceal" my name. (slowly nodding) I eagerly embraced anonymity.

TONI (defensive): Not that three days ago I was the slightest bit worried it would be HIV positive.

TONY: I just didn't want people to think I was worried about being HIV positive.

TONI: Think I was promiscuous.

TONY: Think I was gay.

TONI & TONY (in unison): Think less of me.

TONY: I reaped reassurance from the requisition's check-box inquire of the reason for the HIV test.

TONI: Sex with women?

TONY: Sex with men?

TONI: Blood transfusion? (confused)

TONY: My eyes riveted the requisition, refusing their leave until I saw the "sex with women" box secured.

TONI: I have been unwell of late. (questioning, thinking) A series of minor maladies, that I merely shrugged off as bad luck.

TONY: But I had been always so healthy before, (slowly) and now viewing through my acutely focused retrospectoscope, I recognize these were symptoms of early AIDS.

TONI: Upper respiratory tract infections, fatigue, brittle fingernails, (pause) skin eruptions that were most certainly herpes zoster.

TONY: What am I saying? That my body is already depleted of its immune defenses? That I already have fulminant AIDS? Oh, I wish Norma Evans would call.

TONI: Oh how I wish she'd call.

TONY (pause quietly): I've heard so many times (quoting) "HIV will touch us all."

TONI (still quiet, but getting louder): "We will all suffer its existence."

TONY (getting louder): "We will all have a friend or a loved one who AIDS will torment."

TONI (getting louder): "Will kill."

TONY: But I never thought it would be me.

TONI (stop; look up): Five years ago HIV killed a friend of mine.

TONY (pause, reflective, voice lower): Stuart was a physician... a kind person... a man with whom I swam many pool laps, shared dechlorination, cerebrated solutions to our medical system's frustrations.

TONI: His death, the waste of the second half of his life, spoke to me in decibels beyond the cadavers of celebrities in Hollywood or New York.

TONY (pause): I'm not sure if Stuart was gay. I never considered that he might be gay until AIDS pummeled his person. It wasn't important then. (pause) It's important now.

TONI: How do I tell my parents?

TONY: I saw how they aged rapidly during my sister's recent illness.

TONI: And although my sister is now well, my parents have not recovered.

TONY: I saw how they shared my sister's suffering. I know how deeply they will share mine, long before I suffer.

TONI: I know they will deny my diagnosis.

TONY: Deny it to me.

TONI & TONY (in unison): Deny it to themselves.

TONI: They will demand exceptional therapy. They will insist insight of the best AIDS physicians in the world, for second, third, thirteenth opinions.

TONY: As many as it takes.

TONI: To be treated.

TONY: To be cured.

TONI: They will want to take my HIV from me, (gesturing with hands) give it to themselves.

TONY (pause): My distant death will be their proximate death.

TONI (relieved): I know my sister will be okay. She'll be wonderfully supportive. My friends will be supportive too.

TONY: Though some will twinkle prescience of "wayward encounter", they will stand by me, help when the time comes. Oh, how I wish that phone would ring.

TONI: How do I tell my children?

TONY: Two teenage boys...

TONI: I see their disbelief...

TONY: I feel their pain...

TONI: I refute their refusal to accept my diagnosis. I provide optimistic but reasonable prognosis... as I explain what has happened, (pause) what will happen.

TONY: Previewing that conversation, I admonish words adamantly assuring my HET-er-o-sexuality (defensively), insisting my innocence. (amazed, angry at self) I thought myself enlightened enough not to feel this need, foster this prejudice. I cringe the clarity in my voice emphasizing I contracted HIV from a woman or from a patient. I hate myself for this declaration. It diminishes gay men. (pause and quieter) It diminishes me. It's like a joke I heard and hated ten years ago, in which a man after learning he has AIDS tries to convince his parents he's Haitian. I encourage myself that this heterosexual assurance is for my kids' well-being... not that they'd think less of me... we have always had an open loving relationship, but heterosexual assurance might obviate schoolyard smiles and knowing nods... Why must a heterosexual ribbon adorn death's victory?

TONI: What about my partner...

TONI & TONY (in unison):My life's love?

TONI: Bob.

TONY: Susan. (pause) We hold each other in a magnetic field of oneness.

TONI: Although Bob's been using condoms, could I have given him HIV through my secretions? Could licking or even kissing pass on the virus if you did enough of it? What am I saying? I'm a physician, I should know better!

TONY: How do I tell Susan? I mean, we've only been together for six months, but I feel the sun follow her face, wrapping me in rainbow of her warmth. I carry her with me everywhere... Is there any chance I could have infected her?... We've been using condoms, and they never broke... but I wasn't really super careful. The sheets sometimes are secretion soaked. Could I have infected her? (starts agitated walking) It's unthinkable (negatively shaking head)... it's just unthinkable... I don't care about me having HIV, (pleading) but please, please not Susan.

TONI (cold): I will sever all ties with Bob... with love... with the future. Once the doctor's call (pause) confirms the condemnation I already know.

TONY: Somewhere in the next 24 hours, I will tell Susan that though I love her beyond what I believed love was possible, my HIV means our dream of together must dissolve.

TONI: Bob will tell me that it doesn't matter... and you know, he'll actually mean it. He'll say that he wants to see this through with me... he'll mean that too... But I can't do that to him. It's over. I'll face the future alone.

TONY: Susan can easily find a better partner, much better than me, better than I ever was, ever could be. That's a certainty. She's so bright... beautiful to her soul. I will miss Susan. I will miss her touch, her eyes, her smell, her mind... I miss her already.

TONI (crying; thinks): You know, losing Bob is what hurts most. (hesitates) How do I retreat from his rightness, his rightness for me?

TONY: I am already empty. Empty not feeling Susan's future entwined with mine.

TONI: Somehow we must tune a new attitude, a new permission to admit vulnerability in relationship,

TONY: A new responsibility to protect our partners,

TONI: To protect ourselves,

TONY: A new acceptance that any of us who have ever had sex unprotected by condoms could be carrying HIV.

TONI (pause): Why have I so calmly acquiesced a curtain that an hour ago I would have railed against, protested its possibility?

TONY: Is this calm a shroud, or peace allowed when battle beckons?

TONI: Is this calm carved by my training that emotion lessens objectivity, lessens us?

TONY: Is this calm a façade, or a blanket quenching the immutable verdict's venom?

TONI: This calm is a gift, a gift to sift skill from sentiment, to claim competence required to help loved ones through their imminent anguish.

TONY: This calm will remain till the call,

TONI: Through the call,

TONY: To explain the call

TONI & TONY (in unison): To those I love.

TONI: This calm will remain till the...

Phone rings; Toni and Tony stare at respective phones. It rings a second time. They remain transfixed by the tone, then slowly they symmetrically lift the receivers to their stage lateral ears. Their eyes move up and slightly stage center as they answer.

TONY & TONI: Hello?

The tape comes on. They stare motionless while the doctor's voice is heard.

DOCTOR'S VOICE (fatigue and sadness strung): Hi Tony, so glad you got my message. I have something unfortunate to tell you ... your HIV test... it needs to be repeated ... They wrote the number code on the requisition and your name on the blood tube, so they automatically discard the sample. You can have it repeated tomorrow (lights out).

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HUMOUR

EDITOR: DR. DAVID COLBY

Nuclear Medicine - Beyond Merck

By Ian McIlraith, MEDS 2000

This past summer I turned down a tremendously unprofitable minimum wage job for the tremendously keen undertaking of electives. Armed with a full year of medical education (what more do you need to know?), I felt ready to tackle real medicine in a clinical setting. So, I grabbed the Alumni Binder to find a doctor who would show me the way. One of the listings in my hometown was in Nuclear Medicine. That sounded vaguely interesting, even though I knew absolutely nothing about the field. I promptly consulted the Merck Manual (every PBL tutor's worst nightmare and every student's most valuable, and perhaps only, resource), to find out exactly what this "nuclear medicine" was all about. I found out that it was "the medical application of unsealed radioactive materials for diagnosis and therapy".[1] Great! I was as ready for this as for any PBL session, so off I went.

The little child in me was excited upon entering the Nuclear Medicine department for the first time: "Look at all the neat toys to play with!" I was disappointed to find out that the doctors do not actually get to play with all the equipment--there are technicians that do all that for them. This initial letdown was quickly displaced by panic as the doctor put up a scan and asked me what I thought. For anyone who has never seen the pictures generated in Nuclear Medicine, they are fondly referred to as "fuzzograms" because they are remarkably indistinct to the untrained eye, which is the category I fit into. Not only did I not know how to interpret this result, I did not even know what part of the anatomy I was looking at. Once we had sorted out that it was a lung scan, my mind frantically raced back to the respiratory physiology lectures while the doctor explained the subtleties of this diagnostic modality. The patient had a V/Q mismatch, which was actually observable without reliance upon the eye of faith, and suddenly Nuclear Medicine seemed really interesting!

I spent a fair amount of time with this doctor, and I definitely know a lot more about this field. I also have a deeper respect for it. A few important points to my fellow students, so that you have not totally wasted your time reading this article, and also so that you know more about Nuclear Medicine than the first line of Merck:

1. Nuclear Medicine uses radiopharmaceuticals which are introduced into the patient, so that unlike radiology, the patient is the source of radioactivity. This allows many "fuzzograms" per exposure.
2. While x-rays display anatomy, Nuclear Medicine images display physiology. This is an important distinction, and it hints at the unique uses of this modality; it would be difficult to see a V/Q mismatch on an x-ray.

Nuclear Medicine is typically lumped together with radiology and pathology as a "lifestyle" choice, and indeed it has all the benefits associated with such a specialty. However, there is also the potential for more extensive patient contact (whole, live, conscious patients!) than these other fields. Nuclear Medicine overlaps with Internal Medicine in that thyroid disorders are generally treated by Nuclear Medicine specialists. These doctors are qualified to administer the radioiodine used to ablate hyperactive thyroid glands, and this provides the opportunity for counseling and educating patients.

Perhaps the most important thing that I learned is that Nuclear Medicine is extremely interesting. As Henry N. Wagner wrote, "the excitement of nuclear medicine remains the best kept secret in medicine."[2] You will not find that in Merck.

For those of you who are interested, here are some Internet resources related to Nuclear Medicine:

1. UWO Nuclear Medicine Residency Program page:
   HTTP://johns.largnet.uwo.ca/nucrad/nucres.html

2. A couple good information pages:
   HTTP://www.mallinckrodt.nl/nucmed/noframes/general/nucmed.htm
   HTTP://www.louisville.edu/sahs/nmt/whatisnmt.htm

3. For those who want to view a few nuclear medicine scans:
   HTTP://www.radiology.arizona.edu/~nucmed/title.htm
   HTTP://www.aloha.net/~peters/organ.html

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MEDICAL MYTHS

EDITOR: MATTHEW CRYSTAL

Health Fact or Fiction

By Matthew Crystal, MEDS 2001

Statement: Sexually Transmitted Diseases (STDs) are more common in the Middlesex- London region.

True: STDs are 29% more common in the Middlesex-London region than in the rest of Ontario. Of all the infectious diseases, reported cases of Chlamydia accounted for 84% of the total.[1] Chlamydia is transmitted through unprotected sex with an infected partner. In order to effectively explain the higher incidence in the Middlesex-London region, more research into the specific demographics and diagnostic practices will be necessary. When comparing all of the regions in Southwestern Ontario there is no apparent reason for the rates to be exaggerated in Middlesex.

Statement: Death rates from AIDS have increased almost 300% between the years 1987 and 1992 in both men and women.

False: Mortality rates for women were unchanged from 1987 to 1992. Men, however, have seen an increase in mortality rates approaching 300% for the same time period.[2] Does this statistic imply that women need not be concerned? No, women should be quite concerned because the demographics of the disease are changing drastically as AIDS continues to infiltrate the heterosexual population in our society. The Human Immunodeficiency Virus (HIV) does not target men specifically, but the spread of the disease initially through the gay population erroneously led to the belief that AIDS was a disease of homosexual males.

A demographic analysis of Southwestern Ontario showed that AIDS mortality had the highest incidence in the Middlesex and Essex regions.

Statement: The Southwestern Ontario region has a higher incidence of STDs when compared with the rest of Ontario.

False: Chlamydia has been the most prevalent communicable disease reported in the Southwestern Ontario region, but the incidence rates in this region are still below those for the rest of Ontario. The incidence of chlamydia being reported was 120 per 100,000 which is below the Ontario incidence of approximately 135 per 100,000. The incidence of gonorrhea and AIDS were considerably below the levels for the rest of Ontario. Gonorrhea showed an incidence of 15 per 100,000 and the incidence of AIDS was 3 per 100,000 in the Southwestern Ontario region, well below the Ontario rates of 45 per 100,000 for gonorrhea and 5 per 100,000 for AIDS. Looking at the big picture, STDs were reported 144 times per 100,000 in Southwestern Ontario which is significantly lower than the 190 reported cases per 100,000 in the whole of Ontario.[2]

Statement: Teenagers and young adults are at the highest risk of acquiring a sexually transmitted disease.

True: The highest rates of chlamydia infections, for example, are in the 15 –24 age group. In 1991-92 there were over 1300 reported cases among Southwestern Ontario 15-19 year olds.[1] When comparing the rates of incidence by age in Ontario and Southwestern Ontario, the distributions are very similar, albeit with lower incidences in the Southwestern Ontario region. What causes the rates to be so high within this group? The practice of unsafe sex among this age group is extremely prevalent, accounting for the inflated incidences.

Statement: London residents are well aware of their community's health status.

False: A random telephone survey asking London residents about their knowledge of their own community showed that Londoners underestimated their community's lifestyle and health problems.[3] If knowledge is a key weapon in conquering health and lifestyle issues, then what can be done to prepare Londoners and other Southwestern Ontario residents to become integral components of active health promotion? Public health units have taken the stance that, "The effective control of infectious diseases requires multiple strategies to prevent the occurrence of disease in susceptible populations, interrupt the transmission of infectious agents from one person to another, and treat infected individuals and their contacts." [2]

ABOUT THE AUTHOR

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Education is the key to slowing the spread of infectious agents. Resources include Internet searches, library visits and trips to the local health unit. Public Health Units are instrumental in creating ways of disseminating information to the public as a whole, but it is the responsibility of each and every public health official to promote proper lifestyle choices for their own community and all the patients they specifically interact with. Understanding the socioeconomic conditions of patients is a vital first step toward ensuring that patients consider the options and treatments that are available. The role of the physician is to aid in the prevention of disease transmission and to promote healthy lifestyle choices, while recognizing the limitations of the patient's resources. We must remember that words of encouragement or discouragement by a physician hold a great deal of weight; this responsibility cannot be ignored.

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REVIEW OF MULTIMEDIA SOFTWARE: Urinary Tract Infection in Women

By Mona Orady and Anand Pandya, MEDS 2001

The pain and discomfort of urinary tract infection is well known to women. For some, urinary tract infection may be an ongoing problem, often leading to extensive and costly treatment as well as feelings of frustration.

Therefore, Axia knowledge products introduces a first in health education – a powerful and user-friendly CD ROM software package for women to learn more about the causes, treatments and prevention of urinary tract infection. The goal is to provide an innovative learning environment to uncover the fundamental knowledge and skills needed for people to be proactive in their own health care.

The program is divided into four sections. The Guided Tour is a great place to start to get the most out of the program. It shows you how information is organized and how to navigate through the program. Next, the Overview summarizes key information on urinary tract infection – cause, treatment and prevention. The Learn UTI (urinary tract infection) section integrates multimedia, sound, and graphics to permit the user to develop an understanding of the subject. Finally, the Test Yourself section lets you assess your learning and allows you to move at your own pace.

There are two main themes that make this a blockbuster program. First, it is patient focussed and deals with a sensitive subject matter in a candid, straightforward manner. The program is very comprehensive. The informative presentation is very human because it uses patient-doctor conversations to bring out important points. You feel as if you are in a doctor's office getting your questions and concerns addressed and resolved. Thus, this program has an outstanding potential in health care at an entry level because it could serve as an excellent teaching tool in doctors' waiting rooms and clinics.

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Mona Orady is presently a first year medical student at UWO. Before entrering medical school, she completed a Bachelor of Science degree at McMaster University.

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Creative use of multimedia technology to present medical information is the second theme that makes this program impressive. Throughout the program there are audio and video clips that entertain as well as reinforce the information. For instance, one video clip shows an excerpt from a patient doctor interview that mentions the signs and symptoms of bladder infection. Medical specialists in the field of microbiology, urology, and nearly thirty women have contributed their experiences towards the development of these clips. Furthermore, the use of diagrams and animation gives this program an attractive design that captures the audience's attention. The traditional method of presenting this information would be either in the form of a pamphlet or a videocassette. This CD ROM is revolutionary because it begins a new era in interactive learning through novel and meaningful application of computer technology.

This program has much strength that makes it a top quality product. Its only weakness is a temporary one; there is an "online" button that links directly to the Urinary Tract Infection in Women Internet site. This site is not yet developed, but will evolve over time to include chat sessions, bulletin boards, and news on urinary tract infection, treatment and prevention.

In conclusion, Urinary Tract Infection in Women CD ROM receives our highest commendations for being a pioneer in educating both doctors and patients using computers. There is tremendous potential here to develop other educational CD ROMs in areas like Heart Disease, Cancer and Diabetes.

Evaluation: Two Thumbs Up

Rating: General Audience

Axia Multimedia Corporation
600 – 1040 7th Avenue SW
Calgary, Alberta, Canada, T2P 3G9
Tel: (403) 231-1709
Internet: www.axia.com

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Ω

Medicine on the Internet

By Richard Cleve and Anand Pandya, MEDS 2001

The world-wide web has generated much publicity despite having been formed only seven years ago. The promise of the web continues to be the ability to access the information of the world when you want it. The reality, after all these years, is still inconsistent quality and fragmented information, or incomplete sites. With access to traditional information sources, the health care professional may well ask "why bother with the Internet?" At least part of the answer has come from recent developments as covered by both the popular and scientific press. On the one hand, many people with rare diseases have found the identity, treatments, and support groups that their local health authorities were unable to provide them with. On the other hand, the darker side of the web has been seen with the spreading of illegal, antiquated concoctions, and biased, inaccurate information. It is almost without question that world-wide web users will surf themselves to both good and bad health, increasingly. Therefore, most of the information from the web must be viewed critically by checking (1) What is the authority of the information? (2) Does the information serve the sponsor's interest? (3) Is it fact or opinion?

The goal of this article is increase medical awareness by presenting reputed web-sites.

NEWS

The health care professional should be prepared for patients' questions about late-breaking news, often as seen in the newspaper or more recently cable and web-based sources such as CNN. A number of web-sites carry feeds from various news-wires. Most notable in the area of health-care are (of newspaper fame) HTTP://www.reutershealth.com, and CNN (of cable television fame) HTTP://www.cnn.com/HEALTH.

Rather than the large general news sites, many will find the more specific speciality news sites more useful. Sites such as the Doctor's Guide to the Web at HTTP://www.pslgroup.com/docguide.htm, contain news from conferences and the net in many disease areas. Even more specific, and dealing with this journal's theme, is the Canadian AIDS News site at HTTP://www.cpha.ca/CPHA/canews which specialises in the latest developments in AIDS research and treatment.

ABOUT THE AUTHORS

Richard Cleve is presently a first year student at UWO. Before entering medical school, he completed a Master of Science in Physics at the University of Guelph.

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LITERATURE

Because of the rising costs of publications, and the rapid pace of breaking news, many journals now make available online full articles, search engines, or supplemental material to their paper journals. Links to most of the major medical journals can be found at one of two sites: HTTP://www.webmedlit.com and HTTP://www.medscape.com. The CMA's journal can be found at HTTP://www.cma.ca/journals/cmaj/.

After coming to the realisation that many people who needed access to Medline did not have access, the National Library of Medicine (US), HTTP://www.nlm.nih.gov, made Medline searches freely available to all. This free implementation of Medline contains the complete database; however, it lacks the sophistication of the commercial implementations of Medline.

PHARMACEUTICALS

Arguably one of the fastest changing areas in medicine is the field of pharmaceuticals, including recommendations and alternative therapies. The world-wide web is ideally suited for presenting this kind of material. However, one should be especially cautious here; the use of information from the web requires extreme discretion since many of the sites are either

sponsored by a supply company, or are set up by non-medical authorities. Medicine Net, HTTP://www.medicinenet.com, is a comprehensive site organised by disease, clinical trials, expert-opinions, and by medication side-effects. Featuring an encyclopaedia of drugs, and various discussion groups, Pharminfo, HTTP://www.pharminfo.com, provides a valuable resource. Finally, HTTP://www.pitt.edu/cbw/Internet/ offers information on alternative medical treatments and includes information on AIDS.

RESOURCES

An ongoing project at the National Libraries of Medicine (US) is to create an online anatomical "visible human." Currently, they are still collecting radiographic representations of the human body. Their ultimate aim is a completely seamless interface. HTTP://www.nlm.nih/gov/research/visible/visible_human.html.

The Family Doctor, HTTP://www.familydr.com, and Medscape, HTTP://www.medscape.com, are supersites because they contain reams of practical information aimed at patients, medical students, and the practising professional. Included between the two are medical dictionaries, "clinical pearls", frequently asked question files, and pharmacy information.

Finally, Achoo, based on the popular search engine Yahoo!, strives to be the best medicine search engine available at HTTP://www.achoo.com.

Essentially, the sites mentioned above are interesting starting points for patients who want to play an active role in their health management, and for doctors who want to keep up-to-date in the rapidly changing world of medicine.

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VICARIOUS LIABILITY OF HOSPITALS AND THEIR PHYSICIANS

By Mark Redinger

I. INTRODUCTION

It has been over 17 years since the Court of Appeal ruled in Yepremian v. Scarborough General Hospital, that hospitals were not liable for the negligent actions of their doctors. Since that time there have been significant advances in Canadian tort law, yet the law in many cases regarding vicarious liability of medical institutions has not changed that much. The recent Krever report on the blood inquiry offers us a unique opportunity to examine liability issues for health service workers, and the liability of those institutions that employ them. The size and scope of medical services is staggering by any account. Nation wide the consolidated federal, provincial and territorial health expenditure tops almost 47 billion dollars. Over 10% of the population in Ontario alone is employed in health services, and the province spends an average of $2,614 per patient. The Krever inquiry demonstrates the potential for mishaps in the system and the widespread effect of those mistakes on citizens.

This paper will examine the liability issues involved for medical workers, doctors and students employed in health services. Specifically, it will examine the concept of vicarious liability and circumstances in which liability for medical mishap in the course of employment can be transferred or imputed to hospitals or health organizations such as the Red Cross. It will argue that in many cases, liability for medical mishap should rightly be imputed to hospitals or medical organizations and that the present view of practitioners as independent contractors is outdated.

Initially it is necessary to define vicarious liability as it is legally understood. The doctrine of *respondeat superior* or vicarious liability is defined as "the imposition of liability on one person for the actionable conduct of another, based solely on a relationship between the two persons." In an employment context, vicarious liability deals with the degree to which an employer can be held responsible for the acts of his/her employee. Or more simply, whether an employer can be held liable based solely upon the relationship between the two parties

ABOUT THE AUTHOR

Mark Redinger is a third year Law student at the University of Western Ontario. He graduated with distinction from the University of Toronto in 1995 with a B.A. in Public Policy and Administration and Comparative Politics. This upcoming semester he will be participating in the NAFTA exchange, at the Washington College of Law in Washington D.C. Mark will be articling in 1998-99 at the Toronto firm of Chaiton & Chaiton.

II. OBJECTIVES

As Justice Blair correctly recognized in Yepremian, the acknowledgment of a duty of care in situations invariably involves a policy decision. When courts and legislatures assign liability it is usually intended to accomplish two tasks. At one level the imposition of liability is intended to compensate injured parties at the expense of the party responsible. At a second level liability is designed to deter prohibited or unwanted behavior.

For the employer, vicarious liability is usually imposed for one of four reasons. First, the employer is likely to have created the circumstances in which the employee acted, and should bear responsibility for it. Second, the employer is in the position to minimize the act by allocating certain staff to specific duties. Third, the employer is in a position of authority and is able to discipline the employee for wrongdoing or profit from good work. Fourth, by imposing liability, it is hoped that employers will take appropriate measures to avoid liability situations. A more cynical view promoted by some authors may be that vicarious liability is imposed simply to satisfy judgments that ordinary employees may not be able to do. This 'deep pocket' analysis has evolved from a belief that many employees are judgement proof and may not have the assets in order to satisfy large law suits.

Critics of vicarious liability maintain that instead of acting as a deterrent, employers take a distribution theory approach to liability issues. It is argued that employers are inclined to simply pass on the costs of insuring employees down to the customers in the form of higher prices. It must be noted however that such decisions take place within the context of the market place and are based on an assessment of the willingness of customers to shoulder those extra costs. A vicarious liability model does not prevent employers from suing offending employees for indemnification in order to recover the costs of litigation.

III. VICARIOUS LIABILITY/*RESPONDEAT SUPERIOR*

Currently, there are three requirements that must be satisfied in order to impose vicarious liability upon an employer. First, there must be an employment relationship; second, there must be fault in the legal sense; and third, the act of the employee must have taken place within the scope of employment.

Employment Relationship

The first threshold to be addressed is whether the parties are in an employment relationship. In Armstrong v. Mac's Milk Ltd , the High Court of Ontario considered whether there could be an employment relationship in the

absence of a written contract. The court concluded that whether a party was in a employment relationship was determined by examining the content of the relationship between the parties. Specifically, Holland J. applied a "control test" to look at whether the individual was subject to the control and directions of the employer in respect to how the job was to be completed. Justice Holland noted however that changes in corporate structure such as the advent of independent contractors could make that test invalid. In those circumstances it would be more appropriate to apply an "organizational test" to examine whether the individual's duties formed an integral part of the business.

In the medical context, identifying an employment relationship is a critical threshold to overcome and will depend on the role that is exercised by the individual in question. Hospitals will normally be responsible for the actions of their employees; but who is a hospital employee? Nurses are usually employees of the hospital, as are orderlies, since they are supervised by the hospital and paid directly by the institution. But what about temporary positions, or people paid by third parties that are brought in from the outside to perform services? The law is not as clear in these situations, and an analysis must proceed on a case by case basis. For example, medical Residents have been considered employees even though there may not be the same degree of control exercised by the hospital as on an orderly or nurse. In so doing, the court has given consideration to their status within the hospital and the agreement between the hospital and the university.

Current Canadian law does not recognize hospitals as being liable for the actions of doctors in their professional duties. Physicians who are accredited to practice are not considered employees of the hospital to whom vicarious liability applies, but instead are considered independent practitioners. The present law that insulates hospitals from liability for the acts of doctors is problematic as employment law has now expanded greatly since the 1980's and under current tests it may fail. By virtue of being the workplace the hospital exercises a great deal of control over the doctor in maintaining a site, granting access to facilities, and scheduling. In Brown et al. v. YMHA Jewish Community Centre of Winnipeg the Supreme Court of Canada considered the definition of 'employee' under the Payment of Wages Act, S.M. 1975, c.21, and the Construction Industry Wages Act R.S.M. 1970 c. C190 (am 1980-81, c. 38, s. 3) in Manitoba. The court concluded that 'employee' was a broad and inclusive term. In determining whether an employment relationship existed it was not necessary to prove that there was a contract, or that the employees were paid by the employer directly. However, the court still required that the employer control and direct the employee to evidence employment. In addition, recent cases have also concluded that neither payment by an employer, nor evidence of a contract is determinative if finding an employment relationship. These factors combined may serve to demonstrate an employment relationship in a situation traditionally excluded from that designation.

Fault

The second threshold that must be overcome is whether the employee was at fault in the matter. If there is no fault in a negligence sense, then the courts will not impose liability upon the employer for the employee's acts. Vicarious liability is "...still an action for negligence, and the ordinary rules of negligence liability are still applied to it..." Negligence of the employee, especially a medical employee is a question of fact that must be determined by the courts.

Much has been written about medical negligence or malpractice and this paper will not expand upon that wealth of information. Aside from stating that under a vicarious liability model, the analysis of malpractice will not change. The law does not require that doctors and hospitals perform miracles in the care of patients. Courts instead question whether doctors and health care workers have exercised a reasonable amount of care that is commensurate with that provided by other practitioners of the same experience and standing. In cases against hospitals alleging vicarious liability for hospital employees, the plaintiff has focused upon determining whether the hospital has been negligent in its care, either through overlooking details or otherwise.

Scope of Employment

The third threshold, and the most difficult to prove, is whether the employee's conduct was within the scope of their employment. For sound practical reasons employers are not ordinarily responsible for acts committed by their employees while not under their control or supervision. The recognition of vicarious liability for hospitals does not create a new level of tort analysis. Thus, even if the court recognizes vicarious liability in application to the doctor,

hospitals will still not be responsible for acts committed by doctors, nurses or orderlies employed by a hospital that are considered outside the scope of employment. Understandably, determining what constitutes the scope of employment has been the subject of much litigation.

In Jennings v. C.N.R. the British Columbia Court of Appeal [hereinafter the B.C.C.A.] considered whether a conductor who assaulted a passenger while collecting tickets acted within the scope of his employment. The B.C.C.A. concluded that the collection of tickets was within the scope of his employment. The court went on to conclude that a carrier owed a clear duty of care to its passengers in order to ensure their safety, and thus had a duty to restrain the conductor's conduct where it conflicted with that duty. In Lockhart v. Canadian Pacific Ry. Co. the Supreme Court of Canada considered whether the approval of the employees' method was necessary to render an act within the scope of employment. In its decision the court held that liability would extend to an employer even though the manner in which the business was being carried out was contrary to express instructions. The rule in Lockhart further restricts the ability of employers to escape liability for employee acts.

The court in Yepremian expressly rejected this analysis. Instead the court has responded by holding that the hospital owes no duty of care to the patient for the provision of medical care as practiced by a doctor. Thus, negligent medical acts carried on by doctors in the hospital, under the hospital's supervision, and with the hospital's facilities are not within the scope of employment within the hospital.

(i) Outside the Scope

Not every act of an employee will be imputed to an employer. The following cases illustrate situations in which the court determined that the employees acted outside, or independent of their employment. In Consolidated Mining v. Murdoch, the Supreme Court of Canada (SCC) held that an employer who carried on operations at a remote site, was not liable for the fire started by his two employees. The court concluded that the scope of employment was contained in the employment contract which, in this case, specifically excluded the situation in which the fire took place. This reasoning was upheld by the Supreme Court of British Columbia in Barrett v. The Ship "Arcadia" et al. In that case an assault perpetrated by an officer steward posing as a passenger steward was deemed not to be the responsibility of the employer. In its reasoning the court concluded, like Jennings, that a carrier was not absolutely liable for acts of its employees, but was responsible to take all reasonable steps to safeguard its passengers. Barrett did not disturb the courts earlier position that a carrier would be liable if the act contested had been conducted in the scope of employment. In so doing the Supreme Court of British Columbia has maintained a key element of vicarious liability, namely, the requirement that the impugned act be found to have occurred not only while the individual is employed but within the scope of their employment.

Tests

In addition to the aforementioned criteria the court has expanded the definition of the employee – employer

situations through the development of several common law tests. These tests are designed to look at the totality of the employee-er relationship in order to determine whether an employment relationship exists beyond terminology.

IV. ANALYSIS

From the above discussion it should be clear that courts now look beyond mere titles in order to determine whether an employment relationship does exist. The totality of the working conditions combined with the perception of an employment relationship may result in a sufficient finding of fact in order to justify the imposition of liability. In terms of doctors it may be argued successfully that sufficient control elements exist to make hospitals liable for their negligent conduct. In Yepremian, where the negligent act of an Internist resulted in brain damage, the plaintiffs were successful at trial on the basis that the hospital owed a "non-delegable duty of care to the patient." The Court of Appeal reversing, held that there was no evidence of such a duty of care being owed. The majority also found that the Internist was an independent contractor by virtue of the fact that he was not paid directly by the hospital, he billed OHIP for services, even though he was provided with space by the hospital and was allowed to make use of hospital facilitates.

We will never know what would have happened had Yepremian been appealed to the Supreme Court. However, the minority decisions both made strong statements in favor of recognizing such a duty. In particular Houlden J.A. concluded that the standard of review applicable to hospitals should be commensurate with their role in present day society. Yet, to date Yepremian has not be overturned successfully and has in fact been followed in

several cases. In Papp v. North York Branson Hospital the court held that even in team work situations where both doctors and nurses were working together, the hospital could not be responsible for the negligent acts of the combined team. One should note that in the present political climate of accountability, where the public is often referred to as 'customers' and 'clients' of public services, many if not most citizens would be surprised to learn that upon admittance to a health care facility, the doctor and not the hospital was liable for negligent conduct. American authors have concluded, correctly I believe, that more often than not, patients view both the doctor and hospital as a single body with the doctor acting as an agent for the institution.

Doctors and medical institutions should not be afraid about accepting a vicarious liability model. Such an action would be in line with policy objectives and likely reflect the reality of hospitals today. It is submitted that by placing the responsibility upon the hospital, courts and legislature would be placing the burden to avoid liability situations upon the body best able to deal with it. Hospitals are probably in the best position to discipline doctors by restricting hours of work, and hospitals administrators are probably in the best position to allocate individuals in order to minimize potential problems. Further, vicarious liability may serve to streamline the system by providing a singular body accountable to the patient. All these efforts combined may in the long run serve the patient better by providing a higher quality of guaranteed service by the institution that most patients would likely naturally identify as bearing that responsibility. While opponents of recognizing vicarious liability for doctors may argue that hospitals are ill equipped to deal with that responsibility, it must surely be noted that hospitals are already vicariously responsible for the acts of employees. Further, the imposition of liability would not remove the ability for the institution to seek indemnification from the doctor for negligent acts.

V. CONCLUSION

It is not difficult to measure when employers will be held liable for the actions of their employees. Given the range and scope of decisions, employers can "look forward" to being held responsible unless they can satisfy the court on a narrow band that they should not be held liable. For hospitals and health care facilities the ability to avoid liability is greater when it can be successfully argued that the individual is an independent contractor. As demonstrated, this may not be a reflection of the reality practiced daily in Canadian hospitals, nor what the public would expect of them. For the plaintiff in a malpractice situation he/she must establish more than just employment, and fault, but also sound policy reasons as well in order to assign liability against the institution. The argument on behalf of the hospitals is easier to demonstrate as currently doctors are not considered employees. Thus, unless there is a movement towards assigning institutional liability the current system is unlikely to change. Ω

INTERVIEW WITH DR. MICHAEL J. RIEDER, RECIPIENT OF THE 1997 DOUGLAS BOCKING AWARD

By Helen Lewandowski, MEDS 2001

Dr. Michael J. Rieder is a medical researcher and pediatrician who is also highly involved in medical education. Aside from his research in the area of Pharmacology, and his work at the Children's Hospital of Western Ontario, he is the Chairman of the Phase 4 (Clerkship) Committee at the Faculty of Medicine. He is also the father of three boys aged 14, 12 and 7 years, whom he refers to as his "treasures". His interests outside of work include the American Civil War, mountain-bike riding and cooking for his family. He is also a fan of Baroque music and enjoys the poetry of Rudyard Kipling.

Recently, Dr. Rieder was awarded the Douglas Bocking Award by Western's Faculty of medicine. This is a senior teaching award, given in the Faculty, at graduation, by the graduating class and the Dean's office. Receiving this award came as a surprise to Dr. Rieder: "I was surprised that I won it because it's traditionally won by people who do a lot of teaching in first and second year and I don't see anyone in the class until third year. So it's not an award that someone in my line of teaching would normally win, which is why it was a big honor".

Dr. Rieder has also received numerous awards outside Western. He is a distinguished researcher in the field of Pharmacology, and his research has focused on adverse drug reactions, with a special interest in HIV. Dr. Rieder was designated Young Investigator of the Year by the Canadian Society for Clinical Pharmacology in 1994, and received a similar award from the American Society for Clinical Pharmacology in 1996. He has also done work in the area of medical education, which was acknowledged this past year when he was appointed Harvard Macy Scholar at Harvard Medical School's Macy Institute of Medical Education. This scholarship brings together medical educators from across the U.S.A. and the world to focus on medical education, and Dr. Rieder was the first Canadian academic to ever receive it.

ABOUT THE AUTHOR

Helen Lewandowski is a first year medical student at UWO. Before entering medical school, she earned a Bachelor of Science degree in Psychology from McGill University.

THE PATH TO LONDON

What were the events that led up to you coming to Western?

My university career began at the University of Saskatchewan in Pharmacy. However, in my second year, I realized that although I wanted to do research and liked working with people, I didn't like the commercial aspect of Pharmacy. So I applied to medical school in Saskatchewan, was accepted, and after graduation in 1980 went to Wayne State University in Michigan to do my Pediatric Residency. I then came back to Canada and did a Fellowship in Emergency Medicine at the Hospital for Sick Children in Toronto. During my Residency, I had an interest in pharmacology since my whole family is in Pharmacy except for me. I got interested in clinical pharmacology, so I did my Ph.D. in Pharmacology at the University of Toronto. After that, I was looking for a staff job and London seemed most attractive.

Why London?

It was a combination of things. To be blunt, I liked the size of the city. I'm from a small town of 700 people, and both my wife and I are small town people so we like a smaller city. I like the feel of a university town, which London is. I turned down a job at the Hospital for Sick Children at U of T to come here because the research opportunities were broader here than in Toronto. My interests are immunity and immunopharmacology, and my research career here has done quite well.

IMMUNOPHARMACOLOGY AND ADVERSE DRUG REACTIONS

Could you describe the main research areas that you are currently exploring?

The primary research area that I am involved in is basic science research. More specifically, this includes the study of the role of drug metabolism in the production of adverse drug reactions, with a special interest in HIV. My main interest right now is looking at how drug reactions occur. The current focus is on the sulfa antibiotics and how they produce adverse drug reactions. There are two questions we are working on in this area. One is how HIV

infection influences sulfa metabolism and sulfa sensitivity. A secondary interest is how some of the sulfa metabolites interfere with, or act upon, the immune system. Also on the topic of adverse drug reactions, we are doing some work on agents such as Cephaclor and the antipsychotic Clozapine. That's the primary thrust of our research, but I've also done some work on drug exposure during pregnancy, such as with Cyclosporine. In addition, I have done some educational research, which was mostly related to the evaluation of medical students.

What is the relevance of your research on adverse drug reactions to HIV and AIDS?

It's important in HIV because the most common index case diagnosis for HIV remains pneumocystis carinii pneumonia, and this also remains the most common opportunistic infection in HIV in North America and Western Europe. Sulfa antibiotics remain the drug of choice, and indeed, until the advent of combination retroviral therapy, it was safe to say that the only drugs which were known to prolong life in HIV patients were the sulfas. AZT probably did not prolong life, so the only effective drugs were sulfas. Unfortunately, about 40-50 % of people who take sulfas and have AIDS develop adverse drug reactions, which is about 10 times the incidence of the general population. This is a big problem because of the increase in mortality and morbidity. Why it occurs has been the focus of our interest. We have demonstrated that sulfas can be broken down to reactive metabolites and that there appears to be a difference in the sensitivity of cells to these different metabolites. We knew that this occurs in adults but recently we have also shown that it occurs in children for the first time in the study of adverse drug reactions. This will be published in a couple of months, in the Journal of Pediatrics and Infectious Diseases. So this phenomenon is important, it's common across the age spectrum, and now we're trying to figure out why these HIV cells are so sensitive. We want to know what types of sensitivity occur and how the drug or its presentation can be changed to make it safer. We are also looking at the possible relationship between viral burden and sensitivity of cells to drugs. We know now that viral burden is not constant, it's very dynamic, and we are trying to see if there is any relationship to drug sensitivity.

What are some of the research avenues that you think seem promising for the future of HIV research? Do you think that the virus can be brought under control?

Right now the big thrust is combination retroviral therapy. I'm going to share with you right now that I don't think it's going to work. I think that it will have some success in controlling the disease but if you look at the success rate in clinical practice, it's not as high as in clinical trials, which is no surprise. I think that the virus is persistent, it's cunning and it's simple. It follows a very simple paradigm: it will mutate its way past any retroviral drugs. I think that retroviral therapy is promising, I think that it's important, but I think that it's going to be a constant struggle. There will also be new adverse reactions to these drugs and new problems that will develop, so I think that we are in for a long, tough battle. A viral vaccine is another possibility, and it might work, but I think that HIV will be with us for a long time due to the nature of the beast.

EVALUATION OF MEDICAL STUDENTS

Shifting gears now to your involvement with Clerkship and your research on medical student evaluations, could you describe what that has been about?

Well, I'm interested in evaluations in the broadest sense because one of the things that I don't think we do very well as clinical educators here at Western (and it's not unique to Western, I don't think anyone does it very well) is evaluate students. So I think that the evaluation component of our clinical education is not strong, and I've been looking at different ways to improve that. I think that the problem with evaluating students clinically is knowing what to evaluate, and evaluating things that are clinically relevant. To be blunt, although people get into medical school on the basis of marks, there is no evidence that marks are related to clinical performance. Traditional evaluations using tests and multiple choice questions don't evaluate skills and attitudes, so you need a different way to look at it. There are two possible approaches-one is that you can be a nihilist, and like many clinical educators say that there is no way to evaluate this, so they throw up their arms in despair. I think that we can be more innovative, and that there must be ways to evaluate those skills, so we just have to be more clever about it. The problem with clinical evaluation is that it is a lot of work. Good clinical evaluations do require a concerted effort and a certain mindset on the part of the evaluator. But there are certain problems with that-I think that our system does not reward good evaluators. People who give appropriate criticism are not rewarded for it, and it just results in a lot more work. Therefore, several unsatisfactory behaviors on the part of the students are not monitored, especially in relationships with colleagues. Also, often students are not rewarded for a job well done, and we work hard in addressing that issue.

ON MEDICAL STUDENTS

I think that the two most important attributes in a student are honesty and reliability. If you know when to ask for help, you won't get into trouble. It's important to be able to reach a rational diagnosis in a reasonable period of time, to know how to access information to treat the problem, and to communicate it effectively. I think that that is more important than, say, being able to recite the 20 differential diagnoses for asymptomatic hypercalcemia, for example.

In my mind, the most important characteristics of a clerk are those which define a competent physician. For example, in the pediatric rotation, what's important is being able to talk with a child, talk with the family, and come up with a differential diagnosis of things that are common and important.

In terms of things of value, when someone is functioning clinically, one of the most important things is getting along with people. Medical students are an

interesting bunch in that they tend to be self-selected, but you can't select your patients or the people you work with. So you have to get along with people from a wide range of backgrounds and personalities. That's the reason that in clerkship, if someone has a problem working with clerk A or clerk B, my response would be that they have to work through it. Otherwise, it would tend to become divisive.

THE FUTURE OF CLERKSHIP

Do you foresee any changes in the Clerkship portion of the medical curriculum?

Well, we now have a patient-centered curriculum so Clerkship will probably move towards being more patient-centered, although it could be argued that Clerkship is patient-centered anyway. I think that there will have to be changes in Clerkship due to the changes occurring in London. Ten years ago, we had 3 adult hospitals and 1 children's hospital with 3000 beds, and now we'll have 1000 beds only in the city. So we'll have to rethink about how we do Clerkship. People won't be spending their whole Clerkship in London, that's for sure. I think we'll also have to think about how Clerkship is divided. Does the issue of blocks make sense? I think they probably don't, and that there will have to be some changes in that area. One thing that has recently changed, and that will be a huge advantage for the class of 2001, is that Phase 3 has been eliminated, which means that Clerkship will now start at the end of August and end in September. Right now Clerkship ends in October, then you do your electives and you only have time to do 2-3 electives before the CaRMs match. Now, there will be more time for electives, which will be a major advantage.

Perhaps a key to Dr. Rieder's success in combining his roles as researcher, medical educator, teacher and clinician lies in his personal philosophy: "I believe that when I do a job, I want to do it as best as I can. Personal responsibility and pride in a job well done are the things I was brought up with. I believe in finding the three or four things I like the most in my work and focusing on them". Dr. Rieder's role model is Frederick the Great, a man whose 'singularity of purpose' he finds appealing. He believes that at the Faculty of Medicine and Dentistry at Western "our goal should be excellence... to produce the best undergraduates we possibly can." Clearly, Dr. Rieder is a man with tremendous energy, who truly enjoys what he does.

Ω

CHANGING AIDS-RISK BEHAVIOUR: A Strategy Based On Underlying Psychological Processes

By Dan Mendonca, MEDS 2000

The spread of Human Immunodeficiency Virus (HIV) is a subject which periodically grabs the public's attention. Recently, for instance, the media has drawn a disturbing picture of the sky-rocketing prevalence of HIV in Asian countries. Efforts to prevent a worsening HIV pandemic center on modifying risk behaviours, and education would seem to be the sole instrument for effecting such change. Unfortunately, the issue of educating people about their own reproductive health is a highly contentious one. Most will concede, however, that at the very least, individuals must be made aware of how sexually transmitted diseases are spread, and of how the risk of such infection may be reduced.

During the first decade of the AIDS epidemic, public health officials advised that to protect against HIV, one should either abstain from sexual intercourse, use condoms consistently, or enter into a monogamous relationship with a trusted partner. As a result, monogamy came to be regarded as a substitute for AIDS preventive behaviours such as condom use. Monogamy, however, ceases to be a fail-safe alternative if it refers in practice to a series of sexually monogamous relationships. In fact, it is in these types of relationships that sexual activity is often unprotected, and engaged in with partners who are unlikely to have been tested for HIV.

Safety, in a monogamous relationship, demands that both partners are assured of their own HIV negative status. This may be because neither has ever engaged in unprotected sex (or had exposure to other risk factors), or because both have tested negative for HIV after abstaining from all risky practices during a "window period" of two to six months. These criteria do not characterize most sexually active individuals, who typically became sexually active in their teens, and who are unlikely to have had the same partner since that time. Relatively few people have been tested for HIV, and this is especially true for persons in long-term relationships. Furthermore, HIV testing is not protection against HIV imported as a result of one partner's non-monogamous behaviour during the relationship.

ABOUT THE AUTHOR

Dan Mendonca is a student in his second year of medical school at UWO. Prior to entering Medicine, he completed a Bachelor of Science degree in Biology at the University of Western Ontario.

In the case of heterosexual university students and many other single individuals, much unprotected sexual intercourse takes place within what individuals perceive to be close relationships. The initial practice of safer sex (generally condom use) is eroded with the development of trust in one's mate. Many switch from using condoms to using oral contraceptive pills as the relationship becomes more serious.[1] The emphasis is on contraception rather than on safer sex.

There has been much research on the promotion of AIDS-preventive behaviours. Successful interventions need to involve elicitation research to clarify the specific needs and sensitivities of the target population. As well, they should draw upon empirically validated models of behaviour change. One such research effort, spearheaded at Western, has resulted in the formulation of an information-motivation-behavioural skills (IMB) model for changing AIDS-risk behaviour.[2,3] This model conceptualizes preventive behaviour as being dependent on an individual's information about AIDS, motivation to reduce AIDS risk, and behavioural skills for performing acts related to risk reduction. Currently, the IMB model is being used by educators in London-area high schools, and is the basis for Health Canada's national guidelines on reproductive health promotion for primary care physicians.[4,5]

INFORMATION

Efforts to assess the AIDS prevention knowledge of an individual should seek to identify the spontaneous, ready-to-use AIDS facts which are utilized in real-life situations. To get at this type of knowledge, open-ended questionnaires might be used, as well as focus groups in which individuals discuss their beliefs about AIDS prevention.

Researchers have found that heterosexual university students and members of many other groups invoke "implicit theories of partner AIDS risk" when determining whether or not to practice safer sex. That is, an attempt is made to detect risky partners on the basis of how the partners dress, how they act, and where they are encountered. To the same end, students may use inaccurate AIDS prevention heuristics, or cognitive short-cuts in their decision-making.[6,7] (TABLE 1, 2).

TABLE 1.

Inaccurate Theories Concerning Partner AIDS Risk	
Partner is deemed unlikely to be HIV positive, if...	• there is self-serving attributional bias operating e.g. "Someone to whom I am attracted could not possibly have an STD." • he / she is dissimilar to one's prototype of an HIV-infected person. • he / she has a respectable social network (e.g. from a good neighborhood and family).

TABLE 2.

Inaccurate AIDS-Prevention Heuristics	
"Trusted partners are safe partners."	Once partners begin to trust one another, they decide that they can trust their partner not to have engaged in behaviours that could make them HIV positive. Trust is seen, in effect, as a substitute for condoms or HIV testing.
"Monogamy is safe"	Monogamy is not a substitute for AIDS preventive behaviour unless both partners are completely certain that they are HIV negative.
"It's too-late-anyway"	Many people are unaware of the possibility that a person can have repeated, unprotected sexual contact with an HIV infected person and not develop HIV.

MOTIVATION

Having up-to-date information is no guarantee that an individual will be motivated to practice AIDS preventive behaviour. Individuals may possess negative attitudes concerning condom use (or abstinence), may perceive condom use (or abstinence) as socially stigmatizing or may feel little personal vulnerability to HIV. To reach individuals with negative attitudes towards condom use, one might stress its normativeness in popular culture. To address perceived invulnerability, videotaped scenarios might be shown in which individuals in trusting relationships recount their story of having contracted AIDS through unprotected intercourse.

Persons in monogamous relationships may feel that addressing issues of safety could jeopardize the stability of their relationship. In this instance, individuals might titrate their perception of risk against how intimate they are with their partner.

Motivation may also be explored from a population perspective. It is possible that in certain societies, for example, women might succumb to unsafe sexual activity due to gender based differences in social power, economic dependence on their partners, or normative influences which are opposed to female initiative in sexual matters (TABLE 3).

TABLE 3.

Issues Undermining Motivation to Engage in AIDS Preventive Behaviour
Some discussion topics are seen as potentially harmful to relationships and are avoided if possible. Many believe, for instance, that discussing AIDS prevention will lead their relationship partner to become suspicious about their past or even current behaviour.
An increasing sense of interdependence in a relationship often brings about a shift in focus from self-enhancement and self-protection to relationship maintenance.
HIV testing may be perceived as a "milestone" in a relationship, signifying a new level of commitment which a less committed partner may find threatening.
Entertaining the possibility that one's partner previously engaged in risky and perhaps stigmatizing behaviour is a prospect individuals are motivated to avoid

BEHAVIOURAL SKILLS

It is crucial that informed, motivated individuals obtain the skills necessary for practicing AIDS-prevention. These skills include acquiring and updating accurate information about AIDS prevention, harmoniously yet assertively negotiating AIDS prevention, and exiting situations in which safer sex cannot be negotiated. One should also be able to engage in public behaviours, such as condom purchasing, consulting with physicians and seeking HIV testing. For many individuals, the ability to avoid drinking or drug use before sex has also been related to safer sexual behaviour. Finally, to the extent that condoms are associated with lower levels of sexual enjoyment, individuals might be encouraged to eroticize safer sex.

Behavioural skills that are necessary but lacking should be taught and then rehearsed so that they are readily translatable into real world preventive action. This could include observing models enacting AIDS preventive behaviours, or personally role playing such behaviours and receiving feedback. Interventions delivered to couples rather than individuals offer the opportunity for issues to be processed within a supportive context. Additional skills may be relevant for specific groups, for example, those characterized by ethnicity, sexual orientation, or chemical use status.

CONCLUSION

For the most part, individuals are free to be sexually active. Along with ownership over one's own sexuality, however, comes inherent responsibility. People must take seriously issues involving reproductive health. This is especially true in view of the growing prevalence of HIV infection and other viral STDs. AIDS preventive behaviour can be a sound and effective solution to this growing problem. Consistent condom use and HIV testing must be used for primary and secondary prevention of infection. It has been shown, for example, that the seroconversion rate among AIDS patients and their uninfected partners is very low when condom use is maintained.

While the spread of sexually transmitted disease is preventable, it continues to be a major cause of human suffering and economic loss. Human papillomavirus infection, for instance, is a lesion which can predispose to developing cervical cancer. Similarly, the spread of pelvic inflammatory disease is usually via sexual routes, and can result in chronic pelvic pain or infertility. It is essential, therefore, that physicians motivate their patients to practice prevention.

Educators have found the IMB model for AIDS-risk behaviour change to be a practical tool for teaching STD prevention. The behavioural science community continues to evaluate and improve upon such methods, and their research has proven extremely valuable in the global fight against AIDS.

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THINKING ON YOUR FEET

EDITOR: MASON ROSS

A CASE OF AIDS

By Romy Saibil, MEDS 2000

A 28 year old male presents to the emergency room with a rash, dry cough and a fever. He presented to his family physician three weeks earlier with flu-like symptoms, dry cough and mild dyspnea, although he looked well. He was told he had a community-acquired infection and was prescribed Septra.

Two weeks later, he had lost his appetite. His cough and dyspnea were worse, and he became tachypneaic upon walking for a few minutes. He was referred to the local hospital's Emergency.

While in the Emergency Department, several tests were ordered. The chest x-ray showed bilateral perihilar infiltrates and interstitial disease pattern. His blood gases showed hypoxia. His pO2 was 50 mmHg and his pCO2 was 28mmHg. His CD4+ count was <200 cells/mm^3. His temperature was 38.5°C and his WBC was 1500 cells/mm^3. He did not know he was HIV positive.

Consider the following questions:

1. How does the CD4 count help in monitoring patients who are infected with HIV?
2. What do the bilateral perihilar infiltrates and the interstitial disease pattern on the chest radiograph most likely indicate?
3. What is the pathogenesis of PCP?
4. What is the significance of fever in a person with advanced HIV infection?

ANSWERS TO THE CASE STUDY

1. The stage of HIV disease can be inferred from evaluation of clinical parameters and laboratory tests. Examples of clinical parameters include weight loss and decreasing functional capacity. The CD4 count is an example of one of the lab tests. CD4+ count is a quantitative measure of the lymphocytes to which HIV binds specifically, and which may become depleted as a result of HIV infection. Measuring the number of CD4 lymphocytes has until recently been the primary test for monitoring immune function. In addition to establishing the stage of HIV infection, it helps with establishing a prognosis, and helps to determine the appropriateness of initiating antiretroviral therapy and prophylaxis for opportunistic infections.
2. *Pneumocystis carinii* pneumonia
3. *P. carinii* has such low virulence that the initial infection in an immunocompetent person is suppressed by normal host defense mechanisms and causes no observable damage. In immunocompromised hosts, PCP is usually a reactivation of a latent infection as a result of childhood exposure. HIV-infected individuals are at greatest risk for PCP when the CD4+ T-cell count is <200 mm^3 or <20% of total circulating lymphocytes, or when they have had a previous episode of PCP.
4. Fever is a very nonspecific problem in patients with advanced HIV infection. The development of a new fever should prompt a careful history and physical examination. There are a number of opportunistic infections that may present as a fever of unknown origin in a patient with immune deficiency. In addition to the large spectrum of infections that can produce a fever, there are a number of noninfectious processes, such as malignancies and drug reactions, that should be considered.

ABOUT THE AUTHOR

Romy Saibil is a second year medical student at UWO with a B.Sc. from the University of Western Ontario.

The following section is designed to test and expand your knowledge of Acquired Immunodeficiency Syndrome. How many questions can you answer correctly?

Scoring: [13-15]=superior knowledge, [10-12] = above average, [8-9]= adequate, [5-7]=fair, [1-4]=sub-par.

1. Which one of the following cancers is <u>not</u> associated with AIDS?
   a) Carcinoma of the cervix
   b) Ovarian Cancer
   c) Kaposi's Sarcoma
   d) B-cell Lymphoma
2. Define Cytomegalovirus (CMV)
   a) virus of the genus Cardiovirus found in Africa, South America, and elsewhere.
   b) virus which many people carry for a lifetime without causing any illness, but which in an individual with immune deficiency may infect the eyes, lungs, gut and other organs.
   c) an epidemiologic class of viruses that are acquired by close contact (including sexual contact) or injection and cause persistent infection.
   d) an epidemiologic class of viruses that are acquired by inhalation of fomites and replicate in the respiratory tract, causing generalized reaction.
3. The following are all methods for detecting HIV <u>except</u>:
   a) Southern Blot
   b) ELISA (enzyme-linked immunoabsorbent assay)
   c) Western Blot
   d) Immunoblotting

4. The following are drugs used to interfere with the ability of HIV to reproduce itself, which have also been shown to improve the outcome for many people with AIDS, except:
   a) Zidovudine®
   b) Retrovir®
   c) AZT®
   d) Nizoral®

5. The following are drugs used in treatment of pneumocystis carinii pneumonia, except:
   a) Septra®
   b) Fansidar®
   c) Pentamidine®
   d) Cymevene®

6. Shingles is
   a) a rare, self-limited blistering cutaneous disorder, of unknown origin.
   b) a group of acute infections caused by herpes simplex virus type 1 or type 2.
   c) an acute infectious disease believed to represent activation of latent varicella-zoster virus in those who have been rendered partially immune after a previous attack of chicken pox.
   d) primary cutaneous herpes simplex acquired by direct exogenous infection of traumatized skin lesion, usually associated with localization of lesions to area of trauma and regional lymphadenopathy.

7. Which of the following is not a type of transmission of HIV?
   a) Venereal transmission
   b) Parenteral transmission
   c) Respiratory transmission
   d) Perinatal transmission

8. Reverse Transcriptase
   a) helps integrate cDNA into host DNA.
   b) copies viral RNA genome into double-stranded cDNA.
   c) reverses the process of AIDS.
   d) cleaves the envelope glycoprotein, gp 160, into two subuntis, gp 140, and gp 120.

9. Adverse drug reactions in HIV positive individuals are increased by what factor?
   a) 2X
   b) 5X
   c) 10X
   d) 20X

10. The average time of onset of AIDS from time of contraction of HIV virus is
   a) 2 years
   b) 5 years
   c) 8 years
   d) 10 years

11. *Pnemocystis carinii* is due to
   a) virus
   b) bacteria
   c) protozoa
   d) fungus

ANSWERS TO THE MULTIPLE CHOICE QUESTIONS

1. Which one of the following cancers is not associated with AIDS?
   b) Ovarian Cancer

2. Cytomegalovirus (CMV)
   b) virus which many people carry for a lifetime without causing any illness, but which in an individual with immune deficiency may infect the eyes, lungs, gut and other organs.

3. The following are all methods for detecting HIV except:
   a) Southern Blot

4. The following are drugs used to interfere with the ability of HIV to reproduce itself, and which has been shown to improve the outcome for many people with AIDS, except:
   d) Nizoral®

5. The following are drugs used in treatment of *Pneumocytstis carinii* pneumonia, except:
   d) Cymevene®

6. Shingles is
   c) an acute infectious disease believed to represent activation of latent varicella-zoster virus in those who have been rendered partially immune after a previous attack of chicken pox.

7. Which of the following is not a type of transmission of HIV?
   c) Respiratory transmission

8. Reverse Transcriptase
   b) copies viral RNA genome into double-stranded cDNA.

9. Adverse drug reactions in HIV positive patients are increased by how many times?
   c) 10X

10. The average time of onset of AIDS from time of contraction of HIV is
   c) 8 years

11. *Pneumocystis carinii* is due to
   c) protozoa

VOCABULARY

EDITOR: ZAKIR ESUFALI

MEDICAL VOCABULARY

By Zakir Esufali, MEDS 1999

This section is designed to test and expand your knowledge of medical terminology. How many items can you correctly define?

Scoring:[13-15]=Superior knowledge, [10-12]=Above average, [8-9]=Adequate, [5-7]=Fair, [1-5]=Poor

1. **Hegar's Sign**
   a) Softening of the lower uterine segment during pregnancy.
   b) Dark bluish and congested appearance of the vaginal mucosa during pregnancy.
   c) Softening of the cervix and vagina during pregnancy.
   d) The characteristic facial expression of Hagar.
2. **Roth's Spots**
   a) White or gray soft-edged opacities in the retina seen in diabetes, hypertensive retinopathy, and SLE.
   b) The appearance of the choroid as a red circular area surrounded by gray-white retina, as in Tay-Sachs disease.
   c) Light brown macules characteristic of neurofibromatosis and Albright's syndrome.
   d) Round or oval white spots sometimes seen in the retina in the course of subacute bacterial endocarditis.
3. **Apraxia**
   a) Failure of muscle coordination.
   b) Loss of the ability to carry out familiar or purposeful movements.
   c) Defect or loss of power of expression by speech, writing or signs, secondary to an insult to the brain center.
   d) Inability to recognize familiar objects.
4. **Pseudoseizure**
   a) A seizure which is feigned for the purpose of attaining a specific goal.
   b) An absence seizure.
   c) An attack resembling an epileptic seizure but having purely psychological causes.
   d) An attack resembling an epileptic seizure but which can always be stopped by physically restraining the patient.
5. **Chvostek's Sign**
   a) Electric-like shocks spreading down the body upon forward flexion of the head, typically seen in MS.
   b) A tingling sensation in the distal end of a limb when percussion is made over the site of a divided nerve.
   c) Spasm of the facial muscles elicited by tapping the facial nerve in the region of the parotid gland.
   d) In meningitis, flexion of the hip and the knee upon flexion of the neck.
6. **McBurney's Operation**
   a) A radical operation which includes excision of the vermiform appendix.
   b) Radical surgery for the cure of inguinal hernia.
   c) Urethroplasty for hypospadias repair.
   d) Surgery performed for repair of urinary incontinence in women.
7. **Apoptosis**
   a) Programmed cell death.
   b) Paralytic drooping of the upper eyelid.
   c) Forward displacement or bulging, especially of the eye.
   d) A condition marked by the presence of small whitish ulcers, especially in the mouth.
8. **Weber's Syndrome**
   a) Nevus flammeus distribution over the trigeminal nerve.
   b) Ptosis, strabismus, and loss of light reflex and accommodation secondary to paralysis of the oculomotor nerve.
   c) Premature aging of an adult, with early graying, hair loss and cataracts.
   d) A neuropsychiatric disorder due to thiamine deficiency, most often due to alcohol abuse.
9. **Hypertropia**
   a) Farsightedness.
   b) Strabismus in which there is pronounced deviation of the visual axis of one eye toward that of the other eye.
   c) Inflammation of the eyelids.
   d) Strabismus in which there is permanent upward deviation of the visual axis of one eye.

ABOUT THE AUTHOR

Zakir Esufali is a third year medical student. Mr. Esufali completed an Honours Bachelor of Science degree in Human Biology at the University of Toronto. He is interestedin Internal Medicine and Anesthesiology.

10. Meniere's Disease

a) Deafness, tinnitus, and dizziness in association with nonsuppurative disease of the labyrinth.

b) Progressive, bilaterally symmetrical perceptive hearing loss occurring with age.

c) Psychogenic hearing loss occurring in hysterics and malingerers.

d) Hearing loss due to a defect of the sound-conducting apparatus.

11. Tumescence

a) The production of foul-smelling compounds due to enzymatic decomposition.

b) Any condition marked by the presence of a neoplasm.

c) Swelling.

d) An accumulation of fluid in a sac, cyst, or bursa.

12. Balint's Sign

a) Partial or complete external opthalmoplegia in Grave's Disease.

b) Ocular motor apraxia.

c) Sharp pain associated with pinching of the appendix between the thumb and iliacus in chronic appendicitis.

d) Fine tremor of the tongue observed in sleeping sickness.

13. Cheyne-Stokes Respiration

a) Rapid, short breathing, with pauses of several seconds.

b) Breathing with jerky inspiration.

c) Air hunger.

d) Breathing characterized by rhythmic waxing and waning of respiration depth, with regularly recurring apneic periods.

14. Kayser-Fleischer Rings

a) Pigmented rings at the outer margin of the cornea, seen in lenticular degeneration and pseudosclerosis.

b) Circular ridges composed of collagen fibers surrounding the outer margin Descemet's membrane.

c) White rings seen adjacent to the optic disk in ophthalmoscopy when the retinal pigment epithelium and choroid do not extend to the disk.

d) Rings which are visualized the junction of the conjunctiva and the cornea.

15. Coryza

a) Allergic conjunctivitis.

b) Mucopurulent cough.

c) Acute rhinitis.

d) Painful mucous-containing defecation.

ANSWERS TO MEDICAL VOCABULARY

1. **Hegar's sign: (a)** Softening of the lower uterine segment; indicative of pregnancy, appearing approximately in the sixth week of pregnancy [(b) Chadwick's sign; (c) Goodell's sign].
2. **Roth's Spots: (d)** Round or oval white spots sometimes seen in the course of subacute bacterial endocarditis [(a) Cotton-wool Spots; (b) Cherry Red Spots; (c) Cafe au Lait Spots].
3. **Apraxia: (b)** Loss of ability to carry out familiar purposeful movements in the absence of sensory or motor impairment, especially inability to use objects correctly [(a) Ataxia; (c) Aphasia; (d) Visual agnosia].
4. **Pseudoseizure: (c)** An attack resembling an epileptic seizure but having purely psychological causes, lacking the electroencephalographic changes of epilepsy, and sometimes able to be stopped by an act of will.
5. **Chvostek's Sign: (c)** Spasm of the facial muscles elicited by tapping the facial nerve in the region of the parotid gland; seen in tetany [(a) Lhermitte's Sign; (b) Tinel's Sign; (d) Brudzinski's Sign].
6. **McBurney's Operation: (b)** Radical surgery for the cure of inguinal hernia [(c) Browne Operation; (d) Kelly's Operation].
7. **Apoptosis: (a)** Programmed cell death [(b) Ptosis; (c) Exopthalmos; (d) Aphthosis].
8. **Weber's Syndrome: (b)** Paralysis of the oculomotor nerve on the same side as the lesion, causing ptosis, strabismus, and loss of light reflex and accommodation; also spastic hemiplegia on the side opposite the lesion with increased reflexes and loss of superficial reflexes [(a) Sturge-Weber Syndrome; (c) Werner's Syndrome; (d) Wernicke-Korsakoff Syndrome].
9. **Hypertropia: (d)** Strabismus in which there is permanent upward deviation of the visual axis of an eye [(a) Hyperopia; (b) Esotropia; (c) Blepharitis].
10. **Meniere's Disease: (a)** Deafness, tinnitus, and dizziness in association nonsuppurative disease of the labrynth [(b) Presbycussis; (c) Psychogenic Hearing Loss; (d) Conductive Hearing Loss].
11. **Tumescence: (c)** The condition of being swollen; a swelling [(a) Putrescence; (d) Hygroma].
12. **Balint's Sign (b)** Ocular motor apraxia [(a) Ballet's Sign; (c) Bassler's Sign; (d) Castellani-Low Sign]
13. **Cheyne-Stokes Respiration (d)** Breathing characterized by rhythmic waxing and waning of respiration depth, with regularly recurring apneic periods [(a) Biot's respiration; (b) Cogwheel respiration; (c) Kussmaul's respiration].
14. **Kayser-Fleischer Rings (a)** Gray-green to red-gold pigmented rings at the outer margin of the cornea, seen in progressive lenticular degeneration and pseudosclerosis [(b) Scwalbe's rings; (c) Scleral rings; (d) Conjunctival rings].
15. **Coryza (c)** Acute rhinitis. Ω

FEATURE ARTICLES

A REVIEW OF THE TRANSMISSIBILITY OF THE HUMAN IMMUNODEFICIENCY VIRUS

By Bijan Motamedi, MEDS 1998

Since the first cases of Acquired Immunodeficiency Syndrome (AIDS) were initially encountered in 1981, the disease has spread, and the epidemic is arguably the biggest medical crisis of our time. Due to the latency period (8 to 11 years) and significant under-reporting it is very difficult to accurately estimate the spread of the Human Immunodeficiency Virus (HIV) epidemic. However, the World Health Organisation has estimated that 5 to 10 million people are currently infected with HIV world-wide, and this number is expected to rise to 15 million by the year 2000.[1,2] Despite all the knowledge gained about the pathogenesis of the disease, and means to inhibit its progress, relatively few studies have focused on the transmissibility of the virus and the significance of various risk factors involved. HIV has been isolated from blood, seminal fluid, pre-ejaculate, vaginal secretions, and even urine, cerebrospinal fluid, saliva, tears, and breast milk of infected individuals. However, due to very small concentrations in most bodily fluids, three primary routes of transmission have been identified: sexual contact with an infected person, significant exposure to infected blood or blood products (including needles shared among intravenous drug users), and perinatally from an infected mother to her child. The purpose of this paper is to attempt to answer some basic questions with respect to the transmissibility of HIV. Pertinent literature has been reviewed.

I. SEXUAL TRANSMISSION

Risk Factors For Transmission Among Homosexuals

By far the most common route of transmission is through sexual contact. Among different sexual practices, homosexual transmission of the virus through penile-anal intercourse is the most documented and best understood. This represents over 60% of HIV infections in North America. The association between AIDS and homosexuals was noted with the first few hundred documented cases of AIDS. Even now, in North America, an estimated 30% of the gay population is HIV+.[1,2,3] Many factors have been associated with this link. The principal reason for the higher incidence of AIDS in the male homosexual population is due to the fact that many cases among this group were reported early on, and because of its spread due to a high incidence of multi-partner sexual activity, in a sexually self-contained group. In a study done by Winkelstein et al. within the male homosexual population in San Francisco, the men infected with HIV averaged 61 sex partners compared to 25 for the healthy group.[4]

ABOUT THE AUTHOR

Bijan Motamedi is currently a fourth year medical student at UWO. Prior to medical school he studied Biochemistry at the University of Ottawa.

Aside from the demographics of this population, their sexual practices are also associated with an increased risk of transmission. Male homosexuals engage in a variety of sexual practices, several of which result in exposure to blood and semen. Epidemiological studies have established that among different sexual practices, receptive anal intercourse is associated by and large with the highest risk of HIV acquisition. This can be explained by the high rates of traumatization of the rectal mucosa. Other practices that traumatize the rectal mucosa such as douching, use of dildos, and fisting appear to increase further the infection risk for the receptive partner. Insertive anal sex could also place a man at risk for HIV infection, although the insertive partner would be at lower risk than the receptive partner. Appropriately, these practices have been labelled as "unsafe" sexual practices and are presently practised only with condoms by many homosexual men, or have been abandoned by some. Although clearly safer than anal sex, several reports have also suggested that unprotected oral intercourse may also transmit HIV.[4,5,6,7]

HETEROSEXUAL TRANSMISSION

Although heterosexual transmission still only accounts for 9% of AIDS cases reported in the United States, it comprises the most rapidly growing category.[2,3] World-wide heterosexual transmission is the predominant mode of infection. In Africa, where seroprevalence rates of HIV are highest, acquisition through heterosexual contact accounts for 80% of all HIV infections.[4] World-wide, prostitutes have been the key "vector" of HIV spread.[5] Although the relative efficiency of transmission continues to be evaluated, both male-to-female and female-to-male transmission have been documented.

Information on the heterosexual transmissibility of HIV and risk factors affecting this transmissibility has been obtained from studies of sexual partners of individuals known to be infected, also called "partner studies." The one consistent finding that emerges from all such studies is that male-to-female transmission seems to be considerably more efficient than female-to-male transmission. However, different authors seem to disagree on the relative differences. This lack of consistency seemingly arises, firstly, from the fact that such studies have been very few in number. The second problem is that due to the need to control for the many different variables (e.g., frequency of intercourse, use of condoms, other sexual partners, exact timing of infection) that come into play in designing a randomised-control study, it is very difficult to find a large sample size, which is necessary to strengthen the statistical significance of a study.

There are two methods that can be used to quantify sexual transmissibility through vaginal-penile intercourse. One way is to look at the number of exposures required per infection (i.e., the risk of infection per sexual

intercourse with an infected person). A second method looks at the percentages of steady sex partners of HIV - infected individuals who have acquired the virus from their counterpart. This latter method, despite its weaknesses (frequency of intercourse is not accounted for), is very valuable, less problematic and can easily be done on a larger scale.[5]

I) MALE-TO-FEMALE TRANSMISSION

The predominant mode of documented heterosexual transmission has been male-to-female transmission. Retrospective studies of partners of HIV-infected haemophiliacs and their female sex partners have been particularly valuable because investigators have been able to enroll relatively large numbers of sexually active couples in which the female partners generally had no other risk factors and were much likelier to have a monogamous relationship.[5] Published results of these studies suggest that approximately 10% of the regular female sex partners of infected haemophiliac men have themselves become infected with HIV.[8] Other studies have determined this risk to be as high as 15% or even 30% among other heterosexual groups (non-haemophiliacs).[2,9,10] The risk of infection through a single exposure is extremely low. In a study done by Padian et al., this risk was estimated at less than 0.002 per sexual encounter. However, this risk is very difficult to calculate since although some remain uninfected after hundreds of unprotected sexual contacts, others have become infected after only a few encounters.[11,12] It seems that this risk is different for different populations or geographic locations. For example, as mentioned before, in Africa where the HIV epidemic has the highest proportions, most of the viral spread has occurred through heterosexual transmission, indicating a seemingly more efficient transmission than in North America. A community based cohort study done by Dr. Francis Plummer on prostitutes from one area in Nairobi demonstrated that 67% of 124 uninfected prostitutes seroconverted to HIV-1 over a 30 month follow-up.[13] This dichotomy between the heterosexual transmission of HIV in Africa and the West is a major unanswered question in the epidemiology of HIV-1 transmissibility. These findings all imply that other factors come into play affecting the transmissibility of HIV.

II) FEMALE-TO-MALE TRANSMISSION

Female-to-male sexual transmission of HIV, like transmission of other STDs, appears less efficient than male-to-female transmission. Transmission from infected women to their male partners has been poorly studied. Even in regions where HIV is predominantly acquired through heterosexual contact, few data are available. It is impossible to confidently put a number on the risk of such transmissions. A partner study done by Padian et al. reported only one case of seroconversion among male partners of 72 monogamous heterosexual couples in which the female was HIV positive. However, in a similar study done by the European Study Group on Heterosexual Transmission of HIV, 19 of 159 (12%) of male partners became infected. Higher rates of female-to-male transmission in this study compared to the findings of Padian et al. may reflect a different distribution of cofactors that promote transmission, unacknowledged risks among male partners, and random variation in both studies. Larger studies are needed in order to make more conclusive deductions. [9,12,14]

II. HIV TRANSMISSION THROUGH BLOOD OR BLOOD PRODUCTS

Transfusion Recipients

The exact proportion of world-wide HIV infections through blood transfusions is unknown. In Africa, transfusion recipients have been estimated to account for more than 10% of total HIV infections. In North America, this fraction is less than 3% (this includes individuals infected through tissue transplantation from HIV infected donors), of which 1/3 suffer from haemophilia or another coagulation disorder. In North America, almost all such infections have taken place before the initiation of HIV blood-donor screening programs in 1985. Nowadays, in addition to the laboratory screening tests, blood donors have to fill out an exhaustive questionnaire regarding their lifestyle. This is of course meant to screen out blood donations from people with any risk factors for HIV exposure. Currently, with the additional implementation of HIV-antigen testing, the risk of acquiring HIV infection through a blood transfusion in Canada is estimated at 1/600000. Nevertheless, at the present time, more than ten years after the implementation of HIV screen programs, the impact of HIV infection through blood transfusions is still very real, especially in the haemophiliac population. In 1988, 55% of the haemophiliacs throughout the United States were HIV positive.[2,15,16]

Studies suggest that HIV transmission through blood transfusions is by far the most efficient mode. In one retrospective study 90% of recipients of HIV positive blood became infected. Again, this percentage varies depending on the study, and ranges from 70% to 90%, possibly due to factors such as the stage of the disease of the donor and the amount of transfused blood. Fortunately this mode of transmission is almost eradicated in most parts of the world.[2,15]

VICTIMS OF NEEDLE-STICK INJURY

Transmission of HIV through accidental needle-stick injuries, although very rare, is always a concern among health care workers, especially medical researchers working with concentrated virus. A health care worker's risk of HIV infection is a product of the prevalence of HIV infection in the patient population, the risk of hazardous exposure and the probability of HIV transmission through a single exposure. The amount of blood transmitted through such injuries is minute. Depending on the study, the calculated risk of HIV seroconversion from needle-stick exposure ranges from 0.29% to 0.50%. Depending on the hospital and the precautions taken, investigators have found the risk of percutaneous injury among U.S. surgeons to be between 1.2% to 3.0% per operation. Therefore the risk of HIV infection for a surgeon operating on an HIV positive (unknown) patient is the product of (1.2% - 3.0%) and (0.29% - 0.50%). This results in a calculated risk ranging from 35 per million to 150 per million.[16] Although seemingly low, this risk could reach significant levels when calculated over a period of a lifetime (career). Obviously the only way to reduce the risk is to follow universal blood and body fluid precautions, dispose of needles and other sharp objects properly, and follow other prudent infection control measures.[2,17]

HIV Transmission in Intravenous Drug Users

Transmission of virus through intravenous drug injection is another practice that involves exposure to infected blood. Injection in and of itself is not a risk factor. It is the sharing of needles and syringes with HIV infected individuals that allows viral transmission. Sharing needles

is a common practice among I.V. drug users world-wide, largely driven by legal and economic necessity. As of 1992, I.V. drug users made up 29% of reported cases of AIDS in the United States. This group is also much more likely than the general population to be involved in other high risk behaviours. Therefore, it is very difficult, if not impossible, to estimate the number of people who have become infected solely through sharing needles. Similarly, it is difficult to calculate the risk of infection through one exposure to an HIV contaminated needle. Using a complex mathematical model, in a study done by Kaplan and Heimer, this risk was estimated at 0.0067 per injection episode.[1,18] The risk of HIV infection among I.V. drug users is dependent on the frequency of needle sharing, the number of partners with whom needles are shared, the probability that these partners are HIV infected, and even the manner in which sharing occurs. Among practices associated with a high risk of infection, it is worthwhile to mention the practice of "boothing" (washing out any drug left in the syringe with the user's own blood while the syringe needle is still in the vein), and drug use at "shooting galleries" (sites where drugs are sold and injection equipment is made available for rental or sharing).[3]

III. PERINATAL TRANSMISSION

With the rapid spread of infection among women of reproductive age, perinatal transmission is now a major consequence of the HIV epidemic. According to the World Health Organisation, by 1992, more than 1 million HIV infected infants were born. This mode of transmission is apparently very efficient. One in four infants born to seropositive mothers is infected.[2,3] It has been shown that antiretroviral therapy throughout pregnancy, particularly during labour and delivery, significantly decreases this risk.

Perinatal HIV transmission can occur both *in utero*, or at birth. Identification of maternal factors increasing or decreasing the likelihood of HIV transmission may help to explain differences in transmissions rates. Such factors may include the mother's stage of HIV infection, her degree of immunodeficiency, amount of viral antigen, high HIV replication rate (*in vitro*), as risk factors, and maternal antibodies to viral components as potential protective factors. The mode of delivery itself has also been associated with an altered risk. Any kind of traumatic delivery, such as forceps delivery, or even invasive fetal monitoring, has been suggested as potential risk factors. On the other hand, some have suggested caesarean section as a protective measure as opposed to vaginal delivery that could expose the fetus to a greater amount of vaginal and cervical secretions. Although no hard data is yet available, breast feeding has also been reported as a post-partum risk factor for viral transmission.[2,3]

IV. RISK FACTORS OR CO-FACTORS INFLUENCING HIV INFECTION

Multiple factors probably influence the infectivity of an HIV infected person, or the susceptibility of an uninfected person to HIV infection. An understanding of these factors is potentially important for designing public health interventions that will decrease the incidence of transmission. Several of these factors, such as practices increasing the risk of trauma to the rectal mucosa in homosexual men, or to the uterus in pregnant women, have been discussed.

Of all potential co-factors, the most investigated one is the possible association between HIV and other STDs. More than a hundred studies have looked at this interrelationship. It appears that both ulcerative and non-ulcerative STDs increase the risk of HIV transmission approximately 3-to 5-fold.[14] Several reasons can be postulated for this finding. One aspect of the host response to STDs that may contribute to HIV transmission is the recruitment of inflammatory cells, such as T-lymphocytes or macrophages, where HIV is more frequently found. Similarly, it has been suggested that these inflammatory cells constitute a more suitable environment for HIV invasion. Thus, STDs would increase both the infectivity of the reservoir and the susceptibility of the recipient. Another mechanism by which some STDs might facilitate HIV transmission is disruption of epithelial barriers in the genital tract. The integrity of the genital mucosa or epithelium appears to be an important protection against transmission, and is clearly breached in cases of genital ulcer diseases such as chancroid, herpes and syphilis. Conversely, most studies have found that HIV induced immunosuppression almost certainly is a factor in prolonging the natural history and diminishing the response to therapy of some STDs. At a community level this probable interplay between HIV infection and other STDs' incidence may well underplay the explosive growth of the HIV pandemic in some communities.

Other factors postulated to augment HIV infectivity are both symptomatic disease and early infection. This would be intuitive considering the state of high viremia in either case. Similarly, some studies have suggested that antiretrovial therapy (zidovudine) may reduce infectivity. Several factors have also been suggested to increase the vulnerability of the host. In men, lack of circumcision, and in women, cervical atrophy (such as in post menopausal women) and use of IUDs have both been postulated. Data regarding oral contraceptives is very contradictory. Whereas some have proposed oral contraceptives as a protective factor, others have discussed them as a possible cofactor increasing susceptibility of the host.

It also appears that different strains of the virus could differ in their virulence. Moreover, recent discoveries suggest that innate susceptibility to HIV could differ between people depending on their genetic make-up. Plummer has found that among Nairobi prostitutes, those with certain HLA types seem to be resistant to the virus and do not get infected despite numerous daily exposures.[3,13,16]

Finally at this point it is appropriate to briefly discuss the use of condoms as means of protection. The protective role of condoms towards HIV transmission might seem trivial, however, over the years, this role has been much over-emphasized. Several studies now suggest that although condoms do afford protection to the user, the level of protection is not 100%, and is in fact far from it. A study done by Waller has suggested that this protection could even be as low as only one order of magnitude (x10).[19] Although this finding is extreme, it is important to accept that condoms do not provide full protection. The failures have been attributed to condom breakage, improper use, potential passage of virus through intact condoms, and also more risk taking sexual behaviour when condoms are used.[13]

V. PRACTICES AND MEANS OF CONTACT NOT ASSOCIATED WITH HIV TRANSMISSION

As mentioned before, HIV has been isolated from body fluids other than blood or genital secretions. This finding has raised questions about the transmissibility of virus through casual contacts with an infected person. However, viral detection in these body fluids has been both infrequent and in very small concentrations. There have been anecdotal case

reports of people with no obvious risk factors becoming infected with HIV through what was believed to be "casual" contacts with an infected person. In each case, a better investigation uncovered possible risk factors previously unaccounted for, such as accidental exposure to blood.

Many studies both in the United States and in Europe have looked at the risk of HIV transmission through casual contacts in settings such as household or boarding school contacts of persons infected with HIV. In most settings members had a variety of interactions with the infected person. These included sharing household items, sharing bathrooms, or even helping the person eat or bathe. All of these studies reached the same conclusion: no evidence was found of any HIV transmission to persons lacking other risk factors. Similarly, some studies focused on the possibility of arthropod transmission of HIV. Again no support was found for this mode of transmission.[2,3,20]

This brief overview highlights the magnitude of the problem. Undoubtedly, there is much more to be learned about HIV transmissibility. A better understanding of the cofactors involved, and the role that each plays in the spread of the virus, is essential in order to control the epidemic, and possibly assist researchers in finding a vaccine.

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VIRUSES AND THE IMMUNE SYSTEM: LESSONS FROM HIV

By Dr. Grant McFadden, JPRRI

It has become increasingly apparent that out of the multitude of different families of viruses that have co-evolved with their higher order vertebrate hosts, including Man, only a small minority of these cause any discernible disease. In fact, the normal course of events for most viruses that have propagated for long periods of time within a single host species is for the virus and host to co-exist with each other in a relatively benign relationship that frequently involves little or no outright pathogenesis. As most people know, the retrovirus we now call Human Immunodeficiency Virus (HIV) originally evolved in Old World Monkeys, which harbour many related lentiviruses collectively referred to as Simian Immunodeficiency Viruses (SIVs).The identity of the original simian lentivirus strain that entered the human population to become HIV-1 has not been rigorously established, but in the case of HIV-2 there is a close linkage with an endogenous SIV strain from the Sooty Mangabey monkey. In any case, the best available information is that HIV strains began infecting, and adapting to humans in the latter part of this century. In evolutionary terms, this is very recent indeed. Since most SIVs in their "native" monkey hosts do not cause any disease at all, why does the introduction of this apparently benign primate lentivirus into humans cause such a catastrophic collapse of the cellular immune system? And why are our closely related primates, such as chimpanzees, so apparently resistant to the development of AIDS when infected with the same HIVs?

To virologists, the observation that normally benign viruses, which cause only sub-clinical infections in their native hosts, can suddenly induce severe or even lethal infections in a non-evolutionary host is not new at all. In fact, it is probable that most, if not all, viruses that cause outright disease do so only after infecting new non-adapted hosts. The reasons why a virus might come into contact with a new host can be as varied as animal migration, ecological changes brought about by alterations in environmental conditions, or even chance encounters. Whatever the reason for the virus finding and infecting a new host species, the end result is that the virus now has to survive in the face of a responsive immune system dedicated to the task of preventing the spread of the new contagion. Who will win the resulting tug-of-war? The truth is that the outcome is rarely predictable, but we can uncover some clues as to the dynamics of the struggle by studying other related virus/host battles. One of the great difficulties in dissecting the fundamental mechanisms of AIDS pathogenesis is the absence of a good animal model to mimic the virus/host interplay of HIV in humans. To that end, our lab has spent many years analyzing one particular nonhuman virus/host interaction, namely the infection of rabbits by a pathogenic virus named myxoma virus. These studies allow us to make some tentative predictions about the eventual outcome of the global AIDS pandemic in Man.

Myxoma virus, unlike the relatively smaller RNA-containing HIV, is a large DNA-containing member of the poxvirus family. It is closely related to variola virus, the causative agent for smallpox in Man (before the virus was eradicated by a global vaccination program in the late 1970s). Like so many viral pathogens, myxoma virus was discovered only after the virus made an unexpected leap from its native evolutionary host, the Brazilian jungle rabbit (or tapeti), to a host that the virus had never encountered before, the European rabbit. This host species leap occurred in 1896 when a scientist, Dr. G. Sanarelli, brought a collection of European lab rabbits from Italy to his new research station in Uruguay for some unrelated scientific experiments. Upon arrival in South America, Dr. Sanarelli's rabbits began to die unexpectedly of a previously unknown acute lethal syndrome that we now call myxomatosis. Later, this disease was shown to be caused by a virus harboured within the native tapeti population from the rain forest, and was spread by arthropod vectors, mainly the mosquito. This new virus was studied extensively in the early part of this century, and achieved a certain notoriety when it was used, first in Australia and later in Europe, in an attempt to control the serious overpopulation of European rabbits which had taken over large areas of the countryside, devastating crops and causing widespread ecological damage. Virologists have extensively studied this deliberate release of myxoma virus into a susceptible rabbit population, and our lab in particular has been interested in the molecular mechanisms by which the virus is able to so effectively disrupt the normal immune responses of its infected host.

In humans, HIV infection eventually results in AIDS, but only years or decades following the initial primary infection. In contrast, myxoma virus in European rabbits causes lethal immunosupression with brutal rapidity and kills over 99% of infected hosts within two weeks. Thus, within the initial phases of the myxomatosis epizootic (the animal version of an epidemic) in Australia in 1951-52, there were massive reductions in rabbit numbers, as the mosquito-born virus decimated the rabbit populations. Unexpectedly, however, and within relatively few rabbit generations (less than 10 years), the original strain of highly virulent myxoma virus gradually evolved into new variants of the virus that were dramatically less pathogenic, and which allowed for the survival of a higher percentage of infected rabbits. At the same time, the rabbit populations themselves changed as the selection pressures

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brought on by the extreme lethality of the virus resulted in the repopulation of the infested areas with rabbits that were now much more resistant to the disease manifestations of the virus. The end result was a dynamic series of genetic changes in the virus and the selection of rabbit hosts more tolerant to the virus, that together has culminated in a new less-pathogenic virus/host relationship which continues to evolve to this very day.

So what predictions can we make for the future of the ongoing AIDS pandemic, in terms of how HIV is likely to adapt to the selection pressures exerted by Man? First, it is unlikely that HIV will quietly disappear from the human population. In fact, sequencing studies of the human DNA genome reveal the presence of many retrovirus-like sequences that were acquired during Man's evolutionary past, and there are reasons to suspect that human populations have been subjected many times to virus-driven pandemics similar to that observed in the rabbit populations in Australia. Second, as HIV progressively replicates and mutates within the human population, the severity of the AIDS symptoms will likely evolve to a less virulent disease as the human immune system and the virus become more adapted to each other. However, just because the overt symptomology of AIDS will likely become less severe, there is no reason to suppose that the transmission of virus itself will abate. Rather, it is predicted that as the pathogenesis caused by the evolving strains of HIV diminishes, the percentage of the human population that is actually infected with the virus will continue to increase. Finally, how long can we expect to wait to see this predicted attenuation of the AIDS disease itself? This calculation is quite difficult because of the high mutation rate of HIV and the lack of information concerning the extent of allelic variations of relevant immune loci that might moderate disease progression, but the time scale will almost assuredly be in the order of many human generations. In fact, for all practical purposes, it is difficult to conjure a scenario that actually eliminates HIV from the human population, at least by the development of vaccines and therapies alone. Rather, as advances in the treatment and prevention of AIDS continue to provide real hope for at least the eventual reduction in the absolute numbers of AIDS-associated mortalities, it is a virtual certainty that the HIV virus itself will be with us for the foreseeable future.

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THE EFFECT OF HIV INFECTION ON TUBERCULOSIS

By Ian MacDonald, MEDS 2000

INTRODUCTION

Mycobacterium tuberculosis infects one third of the world's population, resulting in 8 million new cases of tuberculosis (TB) and 3 million deaths annually.[1] Before the emergence of HIV, the vast majority of *M. tuberculosis* infections were kept in check by the host immune response and remained latent for the lifetime of the human host. However, worldwide spread of HIV infection has undermined human defenses against *M. tuberculosis* and presents a serious risk factor for the progression of latent *M. tuberculosis* infection to active TB. In the United States, for decades, there had been a steady decline in the number of cases of TB. By 1985 the decline levelled off and by the late 1980's incident TB cases began to increase steadily. Worldwide, by mid-1995, nearly 6 million persons were estimated to be coinfected with *M. tuberculosis* and HIV.[6] Tuberculosis has become the most common opportunistic infection and the leading cause of death in persons infected with HIV worldwide.

PATHOGENESIS

M. tuberculosis is acquired by inhalation of infectious airborne particles that reach the alveolar air spaces. The inhaled mycobacteria survive phagocytosis by alveolar macrophages and produce a cell-mediated immune response. After ingesting mycobacteria, macrophages present T-lymphocytes with processed mycobacterial antigens. The sensitized lymphocytes then proliferate and secrete cytokines which are able to recruit aggregates of macrophages with increased lytic enzyme concentration and enhanced phagocytic activity. A chronic inflammatory response develops in which the bacteria are killed by repeated phagocytosis.

INFLUENCE OF HIV INFECTION ON PATHOGENESIS

In the normal host, tuberculosis infection usually remains latent, caused by dormant organisms that survive the immunologic response. Reactivation TB occurs when latent organisms overcome immunologic control, as is the case in HIV-induced CD4+ T-lymphocyte depletion. The risk of reactivation in HIV-infected patients with latent TB is more than 25-30 times higher than HIV-seronegative controls.[6] It is also suggested that persons with HIV (regardless of CD4+ cell counts) who are newly infected with *M. tuberculosis* progress to active tuberculosis at a rate as high as 37% in the first 6 months rather than 2 to 5% in the first 2 years.[5] HIV also confers anergy (diminished reactivity to specific antigens) upon the infected individuals, making the interpretation of the tuberculin skin test (TST) difficult. HIV-related enteropathy in infected patients may cause malabsorption of drugs, further complicating the treatment of tuberculosis.

EPIDEMIOLOGY

There are reasons for the increase in the incidence of tuberculosis aside from the emergence of the AIDS epidemic, including the deterioration of public health care facilities and the rise in the number of persons living in crowded settings. However, HIV has had the most serious impact on the epidemiology and natural course of TB. Cross-matching of TB and AIDS registries has provided evidence that the TB epidemic in the United States is, in large part, a result of HIV-associated immunosuppression. Cross-matching the TB and AIDS registries from the 50 state health departments, the District of Columbia, Puerto Rico, and Guam, has yielded estimates that a minimum of 30% of excess TB cases from 1985 through 1990 can be attributed to HIV-induced immunosuppression.[2] The largest increases in incidence of TB occurred in demographic groups and locations in which the prevalence of HIV is highest, particularly in urban areas.

In addition to HIV altering the epidemiology and natural history of TB, TB appears to influence the course of HIV infection. Case-control studies have shown that patients dually infected with HIV and TB had a worse outcome as measured by the development of opportunistic infections and death, compared with HIV-infected patients at a similar stage but without TB.[8] Both groups had a similar level of immunosuppression as measured by the absolute CD4+ lymphocyte count. The effect of active tuberculosis on the HIV-infected patient may be the activation of viral production in cells harboring latent virus, via cytokines from macrophages containing ingested mycobacterial products, and promoting the spread of infection to unaffected cells. This process can lead to a greater viral load, a decline in the number of CD4+ lymphocytes, and an increased risk for opportunistic infection and death.

The rise in the number of cases of tuberculosis in the United States has coincided with an increase in the number of cases of drug-resistant tuberculosis. Drug resistant strains can emerge via incomplete compliance with therapy or an incorrect course of treatment, such as exposure to only one effective drug. When anti-TB drugs are used in combination, growth of organisms resistant to any single drug is prevented by other drugs in the combination.

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Primary resistance occurs when patients are infected with an already resistant strain of tuberculosis; secondary resistance occurs when resistant mutants of an initially drug-susceptible infection appear in the setting of poor compliance. Initially it was thought that most cases of resistance were secondary. However, recent studies have shown that primary resistance accounts for a large number of drug-resistant cases, particularly among the HIV-infected. Coinfection with HIV and drug-resistant TB may help explain the drastic rise in the overall incidence of tuberculosis.

CLINICAL PRESENTATION

The clinical, radiographic, and laboratory features of TB in HIV-infected persons vary depending on the patient's degree of immunosuppression. Infection with HIV is associated with increased dissemination of tuberculosis, increased number and severity of symptoms, and rapid progression to death unless treatment is begun. General symptoms of tuberculosis in HIV-seropositive patients include fever, night sweats, weight loss, anorexia, and chills.

Tuberculosis in HIV-infected patients, as in other populations, is primarily a pulmonary infection. Symptoms include cough, sputum production, dyspnea, and possibly pleuritic chest pain. However, with advanced HIV infection, extrapulmonary disease is a prominent feature. Disseminated disease and lymphadenitis are the most common forms of extrapulmonary TB. It is plausible that extrapulmonary TB indicates a poorer outcome than tuberculosis alone, as the former appears to be associated with a greater degree of immunodeficiency as measured by CD4+ cell counts and the presence of oral candidiasis.

The appearance of chest radiographs from HIV-infected patients with TB may vary depending on the degree of immunodeficiency, although they are often atypical. Most commonly diffuse lobar infiltrates are noted, although focal consolidation may also be present. Cavitary lesions are uncommon however, possibly reflecting the overall immune dysfunction of patients with advanced HIV infection.

Tuberculin skin testing with purified protein derivative (PPD) may be less useful in HIV infected patients with suspected tuberculosis as the sensitivity is inversely related to the degree of immunosuppression. These patients may be anergic due to the decreased delayed-type hypersensitivity (DTH) response common in those with HIV infection, resulting from impaired cell-mediated immunity. In these instances at least two control DTH skin test antigens should be given concurrently with PPD. Generally, all HIV-infected persons with 5 mm or greater induration on PPD skin testing are considered positive and should receive treatment.[3]

DIAGNOSIS

Isolation of *M. tuberculosis* via sputum culture is required for the definitive diagnosis of TB. Given that infection may be present at an extrapulmonary site in HIV-infected patients, clinical specimens other than sputum (e.g., urine, blood, CSF, pleural fluid, pericardial fluid, purulent material, biopsy specimens) should be submitted for culture when extrapulmonary TB is suspected.[3] Newer methods, such as radiometric and continuous culture, allow a more rapid cultivation of mycobacteria than the traditional techniques. The combination of newer procedures and a DNA probe specific for an *M. tuberculosis* ribosomal RNA sequence can identify *M. tuberculosis* in 1 to 3 weeks.[1] This may be clinically significant in identifying TB in HIV-infected patients, due to the accelerated course associated with coinfection. Culture techniques are also important in obtaining the drug-susceptibility profile of a particular strain and in following a patient's response to antimicrobial therapy.

Smears for acid-fast bacilli (AFB) can give an early indication of mycobacterial infection, although a significant number of bacilli per ml of specimen are required for a positive result. There are problems with specificity as the smear does not distinguish between different types of mycobacteria, and atypical species may be present in the immunocomprimised. In general, HIV-infected patients have had lower rates of sputum smear positivity, at least in part because of a lower incidence of cavitary disease.

Newer diagnostic techniques promise rapid detection of *M. tuberculosis* based on the polymerase chain reaction (PCR). This technique relies on gene amplification in which mycobacterial DNA in a clinical sample is extracted, amplified, and identified. With PCR, diagnoses can be made within hours and is generally more sensitive and specific than smear and culture results. This may be important from the perspective of the HIV-infected patient in whom sputum smear results are unreliable due to the potential for extrapulmonary infection.

TREATMENT

Standard antituberculosis drugs are effective for treating tuberculosis in the HIV-infected patient. Most *M. tuberculosis* strains isolated from patients with AIDS are susceptible to first-line agents. A regimen consisting of isoniazid, rifampin, and pyrazinamide for two months, followed by isoniazid and rifampin for 4 months, is recommended as initial therapy. Resistance to any one of these drugs requires longer treatment. Published guidelines by the Center for Disease Control do not recommend longer treatment regimens for patients with TB who are HIV infected and treatment should be prolonged only if there is evidence of a slow response.[7]

The potential for drug-resistant TB should be considered in all patients being treated for TB. This is especially true for multiple-drug resistant tuberculosis (MDRTB), defined as resistance to two or more drugs. MDRTB primarily affects HIV-infected patients and is associated with mortality rates of up to 89%.[7] Most patients die within 1 to 3 months.[5] Patients with MDRTB were also more likely to have pulmonary and extrapulmonary active disease simultaneously, although the latter is still prone to the drug-susceptible regimen, as first-line agents penetrate most tissues well. The treatment regimen usually depends on the pattern of susceptibility, but often includes the aforementioned first-line agents along with second-line agents known to be effective against a resistant strain. These include ethionamide, cycloserine, ofloxacin, and ciprofloxacin.

Directly observed therapy (DOT), in which the patient is observed taking the medication, is meant to ensure compliance with the preventive therapy regimen and thus

reduce the risk of reactivation in the patient. Treatment noncompliance is also a major cause of secondary resistance in tuberculosis, thus DOT can help prevent the increased incidence of resistant TB.

PROPHYLAXIS

Chemoprophylaxis is recommended for any HIV-seropositive patient who is PPD+ with a greater than 5 mm induration, and has no evidence of active disease. Preventive monotherapy with isoniazid can substantially reduce the risk of reactivation among HIV-infected patients who are infected with TB. As has been stated, the HIV-infected individual with latent TB is at extremely high risk for reactivation of active disease. One study reported a tuberculosis incidence of 7.5 per 100 person-years in HIV-infected individuals receiving placebo compared with 2.2 per 100 person-years in those receiving isoniazid.[4] Options for preventive therapy are limited when the likely exposure is to MDRTB, although rifampin has been suggested. Another major concern is the effect of using prophylactic isoniazid alone in contributing to the evolution of drug resistance.

CONCLUSION

The HIV epidemic has possibly been the most important factor responsible for the increased rates of TB. With the advent of increasing drug resistance in strains of *M. tuberculosis* and the spread of HIV in regions with the highest rates of tuberculosis, TB has become the most common opportunistic infection and the leading cause of death in persons infected with HIV worldwide. As the 21st century approaches we are facing the resurgence of an infectious disease once thought to be amenable to eradication. Modern techniques have enhanced our understanding of the epidemiology of TB and provided a more rapid diagnosis and initiation of drug therapy. This approach, along with the traditional interventions of rapid identification and ensuring compliance with therapy, will enable us to control the revival of TB.

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Ω

CHALLENGES OF HIV DRUG COMBINATION THERAPY:
Psychosocial and Practical Impact Reviewed

By J. Scott Turton, ACOL

IN THE BEGINNING...

From the late 1980's to present, advances in HIV therapy have given us a spectrum of medications and approaches with varying degrees of efficacy. The first attempt, AZT, showed some promise in delaying the onset of AIDS but had no real effect in prolonging life. The virus appeared to develop quick resistance and research began on alternative medications. Other drugs (a class of drugs called nucleoside analogues) were developed demonstrating various levels of effectiveness (DDI, D4T). Two years ago, a combination of two nucleoside analogues became the standard therapy and the combination of AZT/3TC became widely used. This combination suppressed viral replication and increased CD4 counts for a year or more in a variety of clinical trials. For those patients who had used AZT prior to this new combination, the virus was able to develop resistance to both medications and only short term benefit was achieved. With the recent development of protease inhibitors (Saquinavir, Ritonavir, Indinavir), a new class of medications was now added to the mixture and the triple combination became standard therapy. Triple and quadruple combinations have recently shown that viral activity can be reduced to undetectable levels and maintained for one or more years. Finally, another class of medications, non-nucleoside reverse transcriptase inhibitors (NNRTI's) are being developed for use in combination therapies.

CHALLENGES OF HIV DRUG COMBINATION THERAPY

Combination therapies (a.k.a. drug cocktails) provide both health benefits and practical challenges to people living with HIV. A review of current literature suggests a number of obstacles to compliance. One commentator writes that taking these medications involves a life change, and stresses that most patients taking the "cocktail" need to organize their lives around a difficult and demanding pill taking schedule.

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Scott Turton completed undergraduate work with the University of Western Ontario and Graduate studies at Wilfrid Laurier University with a Masters degree in Social Work. Scott has worked in the HIV/AIDS field for eight years and is presently Support Services Coordinator with the AIDS Committee of London. Scott is guest lecturer in various courses at UWO and Fanshawe College, has honourary academic status with King's College, and has an active private practice in London, Ontario.

Triple and quadruple drug combinations often involve taking at least twenty pills per day, each medication having differing requirements for timing of doses, and consideration as to whether or not the medications need to be taken with food. Saquinavir, for example, must be taken at eight hour intervals with a small meal. Indinavir, in contrast, must be taken at least one hour before and two hours after eating, three times per day. Depending on the specific drug, directions may stipulate no food and lots of water, low fat food, or high fat food. All of these requirements lead to substantial disruption in normal routine and would often have an impact on adherence to the regimen. Obviously, changes in diet and scheduling of meal times and snacks (or no snacks) becomes an issue. For some, disruption in sleep patterns may occur if the patient needs to wake earlier for a dosing or stay up later than their normal schedule. In regards to dosing schedule, many studies have demonstrated that it is not the number of pills taken per dose, but the number of doses which impacts on compliance levels. These same studies indicate that compliance levels drop off with more than twice a day dosing.[2] At present, the dosing schedules for the drug cocktail remains three times per day, at eight hour intervals.

One must also consider the profile of side effects for the medications as a possible barrier to compliance. Common effects such as nausea, stomach pain and diarrhea may exacerbate compliance. One journalist writes of compliance issues and states that we are assuming that these medical and organizational issues are the main barriers to compliance when in fact, financial cost and lack of support may deter one from even commencing this regimen. Drug costs for protease inhibitors and NNRTI's can well be prohibitive if one does not have access to government drug plans or private plans. The working poor are often in this situation with relatively poor access to life saving medications.

Recent data suggests that compliance is also dependant on environmental, psychological, and social factors. In a recent study Singh and others found that compliance is influenced by a variety of interdependent psychosocial variables which "interact in complex ways to influence overall quality of life and even longevity". In this longitudinal analysis examining the psychological barriers associated with compliance, results demonstrate that within the study sample, non-compliant patients demonstrated "significantly greater psychological distress, emotional disturbance, depression and poor adaptive coping assessed by standard psychological tests".[4] In a related study on stress and stressors, researchers discovered that the average HIV positive respondent in the study appeared to have "more depressive symptoms and more perceived stress than would be expected in the general population". Emotional

factors such as depression, must then be considered by a treating physician as a possible challenge in compliance to a difficult and demanding drug regimen.

WHY IS COMPLIANCE SUCH AN ISSUE?

Quite simply, if there is any interruption of the drug regimen, resistance will occur and the therapy will eventually become ineffective. When people stop their medicine a resurgence of the virus is evident, to some extent, within one day. The trick here is to stop replication by suppressing the viral activity. With the extremely high rates of replication of this virus (approximately 10 billion new copies per day) any interruption of the pharmaceutical pressure on replication through repeat cycles of non-adherence or erratic patterns of compliance likely means that those mutations are going to thrive, and you are going to end up with a whole population of the virus that is resistant to the therapies.[6] Chris Tsoukas of Montreal General Hospital emphatically states that viral load reduction which reduces HIV's replication opportunities is "the only demonstrated way to postpone the development of viral resistance".

ROLE OF PHYSICIANS IN PROMOTING COMPLIANCE

For the most part, commentators believe that medical schools have been inadequate in addressing the issue of recognizing the optimal conditions for compliance to medical advice. Eracker and colleagues note that "few medical schools teach their students to recognize the conditions under which the patient can be expected to follow advice (much less the methods for communicating effectively with patients), or the interview skills needed to assess what the patient knows, believes, or is concerned about".[7] With the reorganization of lives around a difficult pill regimen, Mirken believes that physicians must spend time understanding a patient's life before recommending a specific regimen.[7] Customizing the treatment to a patient's lifestyle, attitudes, and beliefs will impact on the patient's willingness and ability to follow a treatment plan. As previously mentioned, paying attention to emotional factors such as depression may also enhance compliance through active treatment of the emotional condition. Providing referrals for emotional and practical supports (i.e. access to financial supports or payment programs) are also appropriate interventions for patients.

PSYCHOSOCIAL TRANSITIONS

It appears that the introduction of these powerful combination therapies has de-stabilized many people living with HIV from a psychological and social standpoint. In the writer's own practice, a number of people now question their goals and possibilities for long term survival. It is as if, one client states, the world has been turned on its side and something new and frightening has been created. At first thought, logic would dictate that people would rejoice at new possibilities for a prolonged and healthy life. It appears that those individuals who have developed clear self identifications as (a) I am ill with HIV and (b) I will have a shortened life because of HIV, are now being asked to redefine themselves and their world. Derek Scott of the AIDS Bereavement Project of Ontario defines this as an existential crisis. Scott describes the formation of Self as transition between Self-as-uninfected to Self-as-infected.[8] The writer would expand on these Self identifications by stating that we have three identifications happening in this process. First, the individual would identify Self-as-uninfected-and-living. Second, the individual would identify Self-as-infected-and-dying. With the advent of combination therapies, the most recent addition would be Self-as-infected-and-living. Movement from one of these Self identifications to the next would provoke an existential crisis. An individual may question his/her identity, have to refocus goals and beliefs for the future, and in many cases redefine relationships and careers. Scott believes that for people who have resigned themselves to what they have been told is inevitable, "the hope and uncertainty surrounding these therapies can contribute to a feeling of crisis, as once again, the Self and identity undergo a profound shift".[8]

CONCLUSIONS

It appears that the introduction of HIV combination therapies has been a promising medical breakthrough, a practical challenge for compliance and minimizing resistance, and a psychosocial challenge for many living with HIV. It becomes evident that simply giving the medications will not suffice. Complex and interacting variables such as lifestyle, beliefs, resources, and emotional health have to be considered when developing a treatment regimen. A customized approach to treatment is essential for ensuring efficacy of the drugs.

Educators are now struggling with the possibility of relaxed safe-sex behaviours due to the misperception that new drug regimens represent a cure. This is perhaps an area for further discussion and research as mortality rates decrease (due to the effectiveness of the therapy) and infection rates increase.

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Ω

HIV/AIDS:
Epidemiology, Advances in Therapy, Prevention

By Dr. Janet Gilmour, SJHC

INTRODUCTION

As the HIV pandemic continues well into its second decade, the global picture continues to be bleak. According to the UNAIDS there are 8,500 people infected every day. Greater than 40% of these new infections occur in women. More than half of these new infections occur in people between the ages of fifteen and twenty-five years. One thousand children are infected every day. Of the children living with HIV/AIDS, 75% of them have a mother who is also HIV infected. Nineteen percent of the children have a mother living with AIDS and 6% have had a mother die of AIDS.[1] There is no doubt that the impact of this disease continues to be devastating. The developing world has been most hard hit. In parts of Africa, 30-40% of all adults are HIV infected. In Hurare, Zimbabwe, 40% of pregnant women were found to be HIV infected. Life expectancy at birth has decreased by as much as 25% in severely affected countries. Mortality from AIDS continues to increase in the developing world.

In the developed world (Canada, United States, Western Europe and Australia) the rate of new infections has stabilized, and even decreased in some areas. For the first time ever the death rate from AIDS in North America decreased in 1996. Recent developments have led to improved understanding of the pathogenesis of the disease. Several new antiretroviral medications have been developed and are now accessible to some people with HIV. These recent advances have resulted in a sense of cautious optimism.

A cause for considerable concern however, is a recent resurgence of infections among Canadian and American men who have sex with men. Additionally, in Vancouver and Montreal, HIV is currently spreading with alarming speed among injection drug users (IDU's). In Ontario, as well, the situation in IDU's is very unstable. Presently, heterosexual women comprise the group with the greatest increase in rate of new HIV infections. At the HIV Care Programme in London, more than 20% of new referrals are heterosexual women, with no history of IDU or prostitution.

ABOUT THE AUTHOR

Dr. Janet Gilmour is presently Acting Director of the HIV Care Programme, St. Joseph's Health Centre, London. She has been working there since its inception in 1989. Before moving to London, Dr. Gilmour was working full-time in AIDS care at the Immunodeficiency Clinic of the Toronto Hospital. Dr. Gilmour graduated from the University of Toronto with an M.D. in 1983. She completed four years of residency training in Internal Medicine. In addition to her work at the HIV Care Programme, she also attends in the medical wards at St. Joseph's Health Centre and London Health Sciences Centre, Victoria Campus. Dr. Gilmour is the proud mother of four wonderful children.

VIRAL LOAD MEASUREMENT

New methods have been developed that can reproducibly measure the amount of HIV-1 RNA in plasma. Plasma HIV-1 RNA concentration (viral load) is reported as number of copies per ml serum. Viral load has been shown to be the best predictor of clinical outcomes of all markers studied to date.[2] Measurement of viral load has rapidly been adopted as integral to the management of HIV infection. Besides providing valuable prognostic information, change in viral load in response to antiretroviral therapy has proven to be a reliable prediction of clinical response to antiretroviral treatment.[3,4]

ANTIRETROVIRAL THERAPY

The last two years have seen significant changes in treatment of HIV infection. Currently there are three classes of antiretroviral medications available (to a variable degree) to treat HIV infection: nucleoside analogue reverse transcriptase inhibitors (NRTI's), such as Zidovudine, (AZT); non-nucleoside reverse transcriptase inhibitors (NNRTI's), and protease inhibitors (PI). Combinations of medications (three or more) are used to provide greater, more durable virologic suppression.

Clinical trials have shown that combinations of two NRTI's and one PI significantly decrease both morbidity and mortality.[5]

Treatment guidelines now strongly support earlier more aggressive antiretroviral therapy than ever before. 6 Clinical trials are ongoing, studying the effects of initiating antiretroviral therapy at the time of acute infection. For the first time, scientists and clinicians are designing studies to address the possibility of eradicating the virus.

Just one year after protease inhibitors have become widely available, many people have already benefited greatly from their use. Undoubtedly their widespread use has contributed to the decrease in death rates due to AIDS that we have seen across North America. How durable their effects will be remains to be seen. Even so, despite the successes that have occurred, much needs to be done for treatment of HIV-1. Many patients treated with available medications fail to achieve virologic control. Others are unable to tolerate the significant side effects associated with these treatments that, as of yet, do not offer even the hope of a cure. Most limiting is the fact that the majority of the people in the world with HIV infection do not have access at all to any of these medications, by virtue of their high cost. (Approximately $1,000 per month for "standard" triple therapy - see Table 1).

PREVENTION

Success has also been achieved in preventing transmission of HIV-1. Vertical transmission can be reduced by 67% with use of Zidovudine. The vertical

transmission rate of 26% can be reduced to approximately 8% with Zidovudine taken from 14 weeks gestation through labour and deliveries, and administered to the infant for six weeks following birth. [7] Avoidance of breast feeding where there are good alternatives can reduce HIV transmission by 15-30%. HIV testing should therefore be offered to all pregnant women, as part of routine prenatal screening.

Zidovudine (AZT) has also been proven effective at reducing HIV infection (seroconversion) following occupational exposure.[8] To be effective post-exposure prophylaxis (PEP) needs to be initiated as soon as possible following the exposure, ideally within 1-2 hrs. Many hospitals have a standard PEP policy accessible through the emergency department or via occupational health and safety offices. Whether PEP would be effective following sexual exposure has not been determined. The use of barrier prophylaxis significantly reduces sexual transmission of HIV, but does not eliminate it. People whose lifestyle put them at risk for acquiring HIV need to be provided with information about risk reduction and harm reduction techniques.

Thus, while the last few years have seen significant progress in the understanding and treatment of HIV-1 infection, the pandemic is far from controlled. In 1996 alone, 1.5 million people died of AIDS. More than 23 million people have been infected with HIV-1 to date. All estimates predict that by the year 2000 this number will exceed 40 million.

Without a cure or vaccine, the most effective strategy for fighting HIV/AIDS is prevention. Studies done in several countries have shown that prevention programs can result in behavioural changes. More effort needs to be directed toward implementing effective education and prevention programs worldwide.

TABLE 1. MEDICATION EXPENSE

TYPE OF ANTIRETROVIRAL	MEDICATION	APPROXIMATE COST/MONTH
NRTI's	Zidovudine (AZT) RETROVIR	$325.31
	Zalcitabine (DDC) HIVID	193.50
	Didanosine (DDI) VIDEX	184.80
	Lamivudine (3TC)	315.50
	Stavudine (d4T) ZERIT	250.00
Protease Inhibitors (PI's)	Saquinvir (Invirase)	550.79
	Indinavir (Crixivan)	$510.00 (wholesale price)
	Ritonavir (Norvir)	$554.00
	Nelfinavir (Viracept)	Study Med. - Expanded Access
NNRTI's	Delavirdine	Study Med. - Expanded Access
	Nevirapine (Viramune)	Study Med. Expanded Access

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Ω

A GLIMPSE OF THE FACE OF AIDS IN TANZANIA

By Jennifer Hankins and Shane Longman, MEDS 1999

Innocence

Innocence lives in a mud hut on the outskirts of Arusha, Tanzania. The interior is decorated with magazine clippings of white fashion models and black sports stars, taped to mildewing cardboard, and hammered into the dirt walls by Coke bottletops pierced with nails. As a result of his constant diarrhea and frequent lung infections, Innocence is too fatigued and emaciated to work any longer. When he and his wife were clinically diagnosed with AIDS a couple of months ago, she took their four year old daughter and moved in with another man. Innocence has not seen either of them since then. His family does not speak about him any longer, and does not help to support him. They do not visit him, give him food, or help pay for rent or medicines. Occasionally, a neighbour will leave food outside his door.

Richard had two wives. He and one wife died of AIDS-related illnesses a few months ago, leaving his other wife, Gladness, to look after her own five children and the four children born to the deceased wife. Two simple wooden crosses mark their shallow graves in a nearby corn field, easily visible from the mud hut that is Gladness' home now. Gladness' family and friends have abandoned her. Her two youngest children died recently, and her four year old is frequently ill. Her oldest son is not yet of legal age to own land, and Gladness is afraid that when she dies her children and step-children will be forced into the streets when neighbours and relatives divide up her belongings and land.

The making of sugar cane juice for people living with Aids in Arusha

These are some of the stories told to medical and nursing students involved in MedOutreach, a student group from the University of Western Ontario, as they visit the homes of families coping with the daily realities of living with AIDS in Arusha, Tanzania. A 1988 census estimated that there were approximately 1.3 million people in the Arusha region, with about 130,000 people in Arusha town itself.[1] In the summer of 1997, students in MedOutreach had the opportunity to work with Sister Denise Lynch of the Medical Missionaries of Mary (MMM), coordinator of the AIDS Prevention Programme in the Diocese of Arusha. By participating in the MMM AIDS outreach programs, these students were able to see for themselves that many people with AIDS in Arusha suffer in isolation and most die in their homes without adequate care.

Fortunately, the MMM programs are making inroads. In the first six months of 1997, team members from the AIDS Prevention Programme made 2,488 home visits in Arusha to provide emotional support, food, medicine for concurrent illnesses, funds for rent, legal aid, and ongoing education for family and friends.[2] Recently, outreach workers have been bringing sugar-cane, ginger and lime juice along on their home visits. In addition to providing AIDS patients with energy, this juice is produced and will be marketed locally in support of the AIDS Prevention Programme.[3] Besides home visitation, the AIDS Prevention Programme also runs a number of community education programmes, such as "Behaviour Change", for young adults in secondary schools. In an informal survey done in Arusha by the AIDS Prevention Programme,

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about 75% of both boys and girls declared that they had their first sexual experience between 10 and 12 years of age, emphasizing the need for early education about HIV transmission.[2] Of special concern for girls in secondary school is the "sugar-daddy" factor: there are reports of parents who can no longer afford to pay the fees for secondary school advising their daughters to "find someone to pay for them" and giving them condoms to prevent pregnancy. Unfortunately, young girls in this situation who aspire to a future through higher education often find themselves at increased risk of becoming HIV positive.[3]

While working in more remote areas of Tanzania students from MedOutreach had the additional opportunity to learn about the impact AIDS is having in these regions of the country. Cultural practices amongst the Maasai, a proud tribe of nomadic warrior herdsmen, offer insight into the spread of HIV in such locations.[4] It is not uncommon for a Maasai elder to have five wives and 25 living children, all living within a single "boma" (a collection of round mud huts surrounded by a hedge of dense thorns to guard their cattle and goats from lions and leopards). When a warrior from a distant boma comes to visit, it is culturally proper for the village elder to offer the visiting warrior one of his wives for the night. The husband welcomes the prospect of a visiting warrior impregnating his wife since the social status of the elder is enhanced with each new child that is born. This is one reason why the Maasai have been resistant to using condoms.[4]

Another tradition potentially increasing the risk of HIV transmission amongst the Maasai is the practice of group circumcision of young boys. Circumcision is a required ritual in which a Maasai boy must participate in order to become a young adult warrior, or "Moran". Traditionally, the ritual is held in the early morning following a night of celebration and excitement. A group of up to 20 boys, ranging in age from approximately 12 to 18 (ages are actually unknown to most Maasai), are circumcised with the same knife. If a boy flinches or shows fear, both his family and the boy will lose respect in the village. The concern with regards to HIV is that by the time the cohort of boys become circumcised, it is likely that some of the older boys will have travelled to the cities, met with sex workers, and may be HIV positive. Efforts to encourage the use of a separate knife for each circumcision, or at least to clean the blade between procedures, have been met with reluctance because, like many populations, the Maasai are very resistant to make changes to their traditional practices.[4]

Perhaps one of the most disturbing reasons for HIV transmission in the Maasai is a well known "cure" that a Maasai medicine man advised for a HIV positive man. The medicine man had explained to the patient that "the AIDS" in his body could be reduced by half if he were to have sex with a young virgin girl because half of his virus would be passed on to her. If he had sex with enough virgin girls, he would be cured. This "dilution effect" cure dramatically demonstrates the need for education of the Maasai people about HIV and how it is spread.[4]

Various epidemiological studies have shown that the picture of AIDS in Tanzania is serious. As in the rest of sub-Saharan Africa, the majority of HIV in Tanzania is transmitted through heterosexual contact with an infected person.[5,6] Condom use is not widespread; in a recent western Tanzanian study, 88% of men and 63% of women had heard of condoms, but only 20% of men and 3% of women had ever used one.[7] In the Arusha region, HIV prevalence rates are estimated to be higher in women than in men, in urban than in rural areas, in urban areas of low socioeconomic status than those of high socioeconomic status, and in divorced and separated individuals than in married and cohabitating individuals.[8] Factors associated with higher HIV prevalence rates in women in the Arusha region include having travelled outside of Arusha in Tanzania and abroad, having multiple sexual partners, and having sexual intercourse while under the influence of alcohol.[9]

Epidemiology is necessary for revealing the context of HIV and AIDS in Tanzania, but it is the opportunity to meet with people living with HIV and AIDS that gives this picture its colour and texture. Students with MedOutreach were privileged to have a glimpse of how AIDS exists in the Tanzanian setting; the haunted look in Gladness' eyes is a memory that will not easily be forgotten. Clearly, any interventions aimed at reducing the spread of HIV in Tanzania will have their greatest effect if they are able to address the personal experience of living with this disease.

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Ω

THE GEOGRAPHY OF AIDS
Spatial diffusion and the Canadian Experience

By John Ho, MEDS 2000

INTRODUCTION

In 1981, the Western world was introduced to a new disease that seemed distant and unimportant to the general public as it was labeled a "homosexual disease". However, within just a few years of the first recognized cases, Acquired Immune Deficiency Syndrome (AIDS) has gained such a strong foothold that it is now a global epidemic. It is estimated that since 1981, over 6.8 million cases of AIDS, and 1 million deaths due to this disease, have occurred worldwide.[1] Considering that most Western countries are in the later stages of demographic transition, the appearance of an infectious disease as a major cause of deaths is alarming. Already, in 1989 it became the number one killer of men 25-34 years of age in Toronto. In that year, it also entered the top four contributors to potential years of lost life superseding diabetes, chronic lung disease and kidney disease.[2] The spread of the disease has followed a complicated path. Distinct geographical patterns of transmission have emerged which reflect the behavioural patterns of infected people and the interaction networks of the population as a whole. Intricate epidemiologies exist both in and within different regions of the world. Today, we know a lot about the disease but not enough to stop it. In an attempt to better understand this pandemic, the study of this disease through geographical paradigms has been employed.[3]

SPATIAL DIFFUSION

Medical geography has many tools available to help explain the spread of diseases. One of these devices is the spatial diffusion theory defined as the "process by which behaviour of characteristics of the landscape change as a result of what happened elsewhere earlier".[4] Loosely translated for the purposes of this topic, it is the spread of a disease both spatially and temporally from limited origins. The spread of a disease is dependent on several factors including the presence of suitable agents to transmit the disease and appropriate hosts. The nature and spread of the disease usually reflect the geographical and temporal patterns of individual contacts. Spatial diffusion is characterized by a disease origin and changes in the prevalence rate over time.

There are four main models of spatial diffusion: Expansion diffusion, Relocation diffusion, Contagious diffusion and Hierarchical diffusion. Expansion diffusion is a relatively simple model. It simply describes the expansion and diffusion of the disease resulting in more agents possessing the disease. Relocation diffusion is also a simple pattern that is characterized by a change in location of infected agents. Often, relocation diffusion is characterized by great leaps in movement, potentially bypassing intervening populations; however, there is no change in the prevalence of the disease. Contagious diffusion is a slightly more complex archetype involving close contact of individuals. It is often explained in terms of a wave phenomenon in which there is an epicentre with high rates of infection, with a gradual decline in prevalence moving outwards - a distance decay effect. The last type, Hierarchical diffusion is typified by the spread of a disease from a large city to smaller cities over time. This diffusion type is also related to diseases where spread is closely associated with contact of individuals.[4,5,6] These diffusion types are not mutually exclusive; often, disease diffusion processes are a combination of the above types or may have several types occuring at different times depending on the state of progression of the disease cycle.

As with any sort of diffusion, there are situations that may promote the spread of the disease as well as situations that may not favour the movement. Situations that promote the diffusion of disease are known as diffusion networks. These networks consist of the intricate system of people, locations and the links that connect these places -- both physical links and communication links that allow the movement of people, goods and diseases. Factors that serve to prevent diffusion of diseases are known as barriers. There are three manifestations of barriers: absorbing, reflecting and permeable barriers. Absorbing barriers tend to stop a disease from moving at all. Immunization or genetic immunity often has this effect as the disease as unable to seed itself into a population. Reflecting barriers tend to concentrate or deflect diseases towards a certain unblocked area preventing infection of another locale. For example, if two towns are separated by a dense forest, a disease will tend to stay on the side of the forest that it is on and concentrate its effects there. The final type of barrier is a permeable type. This barrier serves to dilute the process of infection or slow down the progression. All of these barrier types can either be physical barriers or cultural practices developed over time to prevent spread of infection. Examples of physical barriers include deserts or vast expanses of water. These physical barriers are not as effective in modern times due to the accessibility of rapid transport over vast distances. Cultural barriers tend to be more effective. These include religious and cultural practices, such as drinking tea in Asia to prevent infection with cholera as the water must be boiled first. As well, these barrier types are not mutually exclusive. Often combinations of the various barriers may exist in an area.

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GLOBAL TRENDS

Worldwide, there are at least three distinct patterns of HIV infection with a fourth one suggested. Pattern I is usually the trend seen in Western countries such as the United States and France. Here, the predominant group initially afflicted with this infection is the male homosexual/bisexual population spread through homosexual sexual activity. As well, an almost simultaneous secondary wave of infection occurs in intravenous drug users. Heterosexual infection initially begins at low levels but increases with time. Women are largely unaffected with ratios above 10:1 male to female. Perinatal infections are rare due to the low prevalence of infected females, however, the pervasiveness is increasing.[7]

Pattern II is typical of sub-Saharan Africa where the epidemic began in the mid to late 1970's. The disease is most prevalent in the heterosexual population with transmission occurring through heterosexual sexual activity. Generally, the male to female ratio is 1:1. Consequently, perinatal infections are also a major problem in these regions.[7]

The third pattern of infection is characteristic of Asian countries such as Thailand and eastern European countries where the epidemic began in the mid to late 1980's. Currently, Pattern III countries account for a very small fraction of cases. However, future projections show disturbingly high levels of infection, greater than those in other parts of the world. It appears that introduction of HIV to these areas is usually through contact with people or blood products from Pattern I and II countries. Prostitutes appear to be the most heavily infected groups in these countries.[7]

The fourth pattern suggested is derived from observations of countries like Brazil and Honduras. This pattern stresses the importance of bisexuals as the major disseminator of the virus spreading the disease from the homosexual population to the heterosexual population. However, caution should be taken as the sexual orientation of these individuals is self-reported. These Latin countries tend to have a 'macho' attitude and describing oneself as bisexual is favoured over being homosexual.[7]

These patterns are broad and general observations. In fact, some countries may have several patterns occurring in different regions or even within the same metropolitan city. As well, the patterns of the disease should be expected to change as the disease makes its course through the population of these areas.[8]

EPIDEMIOLOGY IN CANADA

According to the World Health Organization, Canada had 8,232 cases of AIDS reported at the end of June 1993. Early predictions for the cumulative total of cases were estimated at 11,000 cases by the end of 1993.[9] These reports and predictions must take into consideration the level of completeness in reporting and the delay in reporting which can significantly affect the accuracy of the statistics. Initially, the mode of transmission eluded scientists. However, as the scientists learned more, it became evident that transmission occurred through contact with infected bodily fluids, especially blood and semen.

The major methods of transmission include sexual activity, injection drug use, contact with blood or blood products and through perinatal routes.[9] The prevalence within the gay community was largely due to the "party atmosphere" of the gay lifestyle. The mentality of the gay population at the time included multiple sexual partners, unprotected sex (as there was no risk of pregnancy), and a perception that a cure for most sexually transmitted diseases existed. Initially, all of the cases in Canada were attributed to gay men. However, as the epidemic spread through the community, strong educational programs to erect cultural barriers were initiated. The incidence of new cases amongst the gay community has stabilized and even dropped. Current prevalence levels are approximately 10-15%.[2] However, there are indications of a second, smaller increase in incidence attributable to young gay males who are having unprotected sex.

Since the first cases reported in 1981, the epidemiology of HIV/AIDS has changed drastically. The disease has spread to injection drug users and from there to the heterosexual population. It is reported that the incidence in 1993 was at 2% with regional variations. Recent studies have estimated that the prevalence may be as high as 15-20% in the general population with incidence rates of 6-7%.[2] Other people became infected after receiving tainted blood products, although this sub-group is rapidly declining as blood products are now thoroughly screened in Canada. As women became infected, so did children who were either in utero or breast-feeding. Seventy-four percent of pediatric cases in Canada have been attributed to perinatal transmission as of July 1993.[9] Other sub-populations at risk of contracting the disease are health care workers, although universal precautions have made the chances of being infected extremely low.[9] In an interesting turn of events, HIV/AIDS is now spreading rapidly within the heterosexual population, especially among heterosexual young women. It is clear that heterosexual transmission has become an important contributor in this disease's progression.

THE NUMBERS GAME IN CANADA

Not surprisingly, research and literature into HIV/AIDS is very scarce in Canada. The majority of publications are from the provincial and federal governments. However, this information is sufficient to illuminate patterns and trends in the HIV epidemic here in Canada. According to statistics from Health Canada, adjusted for reporting delays and under-reporting, as of September 30, 1995, Canada had a total of 15,926 cases of AIDS reported. As of December 31, 1995, the provinces hardest hit by this virus were Ontario with 40.6% of cases, Quebec with 31.1%, British Columbia with 17.1% and finally Alberta with 6.2% of cases. Together, these four provinces account for 95% of the cases of AIDS reported in Canada.[10]

Within these four provinces, epidemiological differences exist. Ontario, Quebec and Alberta can attribute approximately 70-78% of AIDS cases to homosexual activity while British Columbia has a higher rate at 88%. The other provinces can attribute 66% of their AIDS cases to homosexual activity. It is interesting to note that Quebec has a significantly higher rate of

females infected (6.0% compared to 1.6% in the rest of the country) and a higher rate of heterosexual infection. This anomaly has been attributed to the high rate of immigrants from Africa where the disease is prevalent in the heterosexual population.[2] Regarding infections occuring in the smaller provinces, there is a greater number of heterosexuals infected compared to homosexuals. This variation in demographics can be ascribed to the lack of large metropolitan cities with large gay populations.

The spread of HIV in Canada largely follows a hierarchical diffusion. These results are similar to findings in Finland and the United States, countries which are in similar states of maturity.[11] The areas in Canada that reported the highest number of AIDS cases (78.1%) in 1983 were in the large metropolitan cities of Toronto, Montreal and Vancouver -- cities with strong international connections. Only six percent of cases were in medium sized cities with populations between 50 000 to 750 000 people with the remaining cases (15.6%) in other areas. However, by the end of 1987, the proportions changed to 63.1%, 21.6% and 15.3% respectively. These numbers indicate the disease originated in urban cores of large cities and gradually spread to suburbs, smaller cities and rural areas. This diffusion process is very similar to patterns seen in other developed countries such as the United States and Finland.[12]

THE SMALLER PICTURE: ONTARIO

While global and national patterns are interesting, they can often overshadow important underlying spatial variations within smaller regions.[13] This is especially evident in Canada due to its sheer size and diversity within each region. According to statistics from Health Canada, Ontario is the province with the greatest number of AIDS cases. This is not surprising as Ontario is the largest province in Canada consisting of approximately 40% of the population. Within the province, it appears as if Toronto was the epicentre. This is expected as the city serves as a major international, commercial and transportation hub. As well, the presence of the country's largest urbanized area contains the country's largest gay community. Although these characteristics were unlike the occurrences found in the United Kingdom, they were similar to those of Helsinki and the Finnish experience.[11,14,15] Due to the tremendous variation in demographics within the province, variations in the spread of the epidemic exist.

Over a five year span from 1988 to 1993, the spread of AIDS moved rapidly in Ontario. Initially, the areas of primary infection were in the urbanized areas of Ontario particularly Windsor, London, Ottawa, Toronto and the rest of the Golden Horseshoe.[16] Within Metropolitan Toronto, the cases were concentrated within the Central Business District, due to the presence of the "gay village". Parts of northwestern Ontario were still devoid of any cases of AIDS. However, by the end of 1993, a significant number of cases appeared in the outlying regions of the metropolitan areas. The most updated statistics show that even the northwestern regions of Ontario are not free of AIDS cases either.[10]

It is interesting to note that although the Central Business District of Metropolitan Toronto still has the highest cumulative number of cases, the number of new cases in this area has actually decreased. In stark contrast, the outlying regions have seen tremendous increases not only in cumulative cases, but also in incidence. This trend appears to be typified by a hierarchical diffusion superimposed by an expansion diffusion. As the initial wave spread from downtown Toronto, it hit other larger cities, appearing to miss intermediate locales. However, as the disease progressed, outlying regions began to feel the effects.[17] The possibility also exists that the movement of AIDS to the more rural parts of Ontario could be due to migration of people diagnosed with AIDS in cities returning to their home towns - a relocation diffusion. This pattern has been documented in North Carolina and helps to explain the rapid diffusion of the disease.[18]

Curiously, the spread of AIDS cases appears to occur along an east-west axis within Southern Ontario. This is possibly explained by migration patterns and the social and family networks in existence in the province similar to situations in New York City.[19] Vehicular traffic along the 401 highway is the busiest in the country with Toronto as the centre of the highway system. Everyday, over 46 000 people travel into the downtown core from the eastern and western areas of the Golden Horseshoe by rail alone.[20] It appears as if the disease followed the network in place to spread to other communities. These observations would be in agreement with those found in Uganda where the disease spread along its trucking routes.[21,22]

Other factors, which may help to explain the initial spread of the disease in Toronto, may include the behavioural patterns of homosexuals in Toronto. In a survey, it was reported that gay men who lived in smaller cities were more likely to live in a relationship than their counterparts in large metropolitan cities. This also correlated with the number of people in monogamous relationships.[23] Thus homosexuals in the urban areas tended to have greater numbers of partners, thus facilitating the diffusion of the virus.

CONCLUSIONS

Geography is a particularly useful tool in medicine, especially in helping to elucidate the current epidemic with HIV/AIDS. Geography is able to illustrate the spatial-temporal variation in patterns of HIV infection and AIDS.[13] As well, it can provide direction for researchers and help predict future trends, thus aiding in effective deployment of scarce health care resources. Lastly, it is able to combine various sources of information from various disciplines and synthesize more useful information than the parts alone. While the current epidemic is disturbing and striking a largely ignorant population, intervention programs can help stabilize the current infection rate, and perhaps someday extinguish this disease. It is obvious that cities play key roles in the dissemination of this disease. However, it is also obvious that the outlying areas are at the greatest risk of becoming infected as HIV makes it way through the population. The general trend of HIV infection and AIDS cases in Ontario thus appears to be following a combination of hierarchical, expansion and contagious

diffusion. The purpose of this paper was to perhaps integrate and synthesize some new ideas in the geography of HIV/AIDS. However, only the "tip of the iceberg" has been observed. There is a tremendous opportunity for further research. More research in Canada can only help bring a better understanding of this epidemic, and help parties interested manage the progression of this disease more suitably.

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Ω

HIV/AIDS IN THE SPORTS SETTING

By Matthew Menon, MEDS 2000

Public awareness of the issue of the Human Immunodeficiency Virus (HIV) in sport grew on November 7, 1991 when Earvin "Magic" Johnson announced his retirement from professional basketball due to his HIV positive status. The statement made by a physician, that a Montreal woman had claimed to have slept with "nearly 50" professional hockey players before she died of AIDS, reinforced that high risk behavior outside of the sporting context could bring HIV into the sport arena.[1] Magic Johnson was not the first professional athlete known to be HIV positive. The death of Jerry Smith, a former Tight End with the Washington Redskins, of AIDS in 1987 didn't capture the same media attention as Johnson's case.[2] The New England Journal of Medicine reported a case of a bodybuilder with AIDS as early as 1984.[3]

Awareness of AIDS in the athletic community continues to grow with the stories of Arthur Ashe, Greg Louganis and boxer Tommy Morrison who recently returned to the ring.[4] A 1992 survey of NCAA institutions reported 8 schools known to have HIV infected athletes and 4 schools with athletes known to have AIDS, one of whom is still playing.[5]

The majority of official statements have concerned three issues: testing of athletes, the participation of HIV positive athletes, and the practice of universal precautions by the athletic health care team.[5] Several groups have published guidelines to address these issues. These include the World Health Organization (WHO), in association with several sports medicine bodies, in 1989. In 1991, The American Academy of Pediatrics published guidelines on HIV in the athletic setting.[6] A comprehensive joint position statement entitled Human Immunodeficieny Virus (HIV) and Other Blood – Borne Pathogens in Sports, was published by the American Medical Society for Sports Medicine and the American Academy of Sports Medicine in 1995.[7] The Canadian Academy of Sports Medicine published its first brochure on this issue entitled AIDS and the Athlete in 1989. This was replaced by a more current, bilingual document: HIV and the Athlete: Question and Answers about AIDS in 1992.[1,8]

The National Basketball Association took the lead among professional organizations in taking responsibility to make players aware of HIV after the Magic Johnson issues arose.[9] On November 19, 1991, the National Hockey League encouraged all league officials to provide HIV testing and counseling but no mandatory testing. The National Football League sent letters to all club general managers, presidents and trainers on December 5, 1991 regarding HIV. This letter stated, "It is important that we all become better informed about HIV and AIDS."

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The consensus reached by all of these groups, athletic or medical, is that there is no need for routine testing for athletes, no justifiable restrictions due only to HIV infection, and that appropriate attention to infection control in training facilities is necessary.[5] Their concern is related more to off–field risk behavior than to risk during competition.[9]

Major sports organizations have been supportive of the HIV positive athlete and in protecting their athletes from infection. They all stress the need for education regarding off-field risk behaviors as the greatest risk to athletes lies in sexual practices and parenteral drug use.[7,9] They also advocate the use of common sense precautions when dealing with bleeding, such as the use of gloves, not reusing towels and bandaging wounds. Most sports organizations have permitted unlimited time-outs to control bleeding.[2]

The NFL's HIV/AIDS policy, in effect since July 6, 1992, is a good example of what most organizations uphold. The aim of their policy is to provide the best possible information to all players and staff. Most of the education is on off-field risk behaviors. They also advocate no mandatory testing and no mandatory disclosure of test results. Policy on disclosure can be complicated as some states require the reporting of positive test results.[10] There is more variance in policies of the NCAA schools where 33 schools have policies on participation of HIV positive athletes. Fifteen schools ban the activity of these individuals in some or all sports according to the 1992 survey.[5]

There are no data for HIV prevalence in any sport group. Using data related to the NCAA age range (18 – 24) we may estimate that there are around 216 athletes in the NCAA with HIV. Actually, intercollegiate athletes may be at a slightly higher risk compared with non–athletic controls due to an increased frequency of sexual partners and the decreased use of contraception in this population.

Nor are there any data assessing the risk of HIV transmission from athlete to athlete, or from athlete to medical personnel. There is only one reported case of an athlete contracting HIV during competition.[11] The authors of the report claim that a 25-year old Italian soccer player bumped heads with an HIV positive player during a game in 1989. This player had tested negative for HIV one year earlier. He denied any risk behavior and claimed to be in a long-term monogamous relationship. This case has been dismissed by the medical and sporting communities as invalid.[9] This case was based on flimsy evidence and there was doubt as to the lifestyle of the player. Experts have dismissed the possibility that sport was responsible for transmission after reviewing all aspects of the case.[2]

There has never been a report of HIV transmission from an athlete to the training staff. It is estimated that for healthcare workers exposed to HIV there is one case of seroconversion for every 250 needle stick exposures. This risk increases with hollow bore needles.

Statistically, we can be certain that there are HIV infected athletes competing at all levels of sport from high school to professional. However, the lack of documented cases is significant considering the known prevalence of HIV.[7] The risk of transmitting the virus, even during contact sport, although

not zero, is far too small to quantify. It may be useful to compare the risk of contracting HIV to that of contracting Hepatitis B which is more common and more likely to be transmitted during sport. As of 1994, there were only 3 reports of Hepatitis B among NFL players.[10] All of these infections were due to off – field behaviors. The only validated case of Hepatitis B transmission during sport was between two high school Sumo wrestlers in Japan in 1982.[7]

The NFL has actually attempted to quantify the risks of HIV infection during a game. They estimate this risk to be approximately one infection per 85 million game contacts.[4] This is about equal to one infection for every million games. The NFL is one of the few organizations that does not necessarily interrupt play due to blood.[10] There is an average of 4 to 5 bleeding injuries per game in the NFL. Most of these are abrasions that do not represent measurable risk. Ninety percent of the body is covered by NFL equipment and uniforms. This further reduces the possibility of exchanging blood during a game.

There was a report in 1984 of a bodybuilder with AIDS.[3] This athlete admitted to a 4 year history of sharing needles to use anabolic steroids once per week. He discontinued this practice two years previously when he contracted Hepatitis B. He denied any other risk factors. This case reinforces that the major risk to athletes is in off-field behavior. It is estimated that 38% of anabolic steroid users inject the steroids parenterally.[4]

According to the 1992 survey, 4% of NCAA schools have routine HIV testing within an education program.[5] Two of these schools have mandatory testing. Seventy-eight percent of NCAA schools offer no testing through their athletic program. The NCAA guidelines recommend against mandatory testing. HIV testing for those at risk should be accompanied by pre-and post-test counseling and an education program. Also, the team physician should be aware that the patient's right to confidentiality prevents disclosure of an athlete's test results to the rest of the team or training staff. Physicians are advised to counsel the HIV positive athlete about transmission and, if the athlete participates in a combative sport (i.e. football, wrestling), they should strongly suggest an alternate sport choice.

At the present time there is no medical or public health justification for screening of athletes for HIV. The process of screening is neither effective nor practical.[2] Such testing would have to be done at least every three months. Also, mass screening for widespread infections among a low risk group leads to a high false positive rate. Although some organizations, such as the Nevada Boxing Commission, require testing of all their athletes, this is contrary to the current recommendations. The best way to deal with this issue is to educate the athletes and then provide testing and counseling for those at risk on a voluntary basis.

Universal Precautions refers to a group of hygienic guidelines used in the handling of potentially infectious bodily fluids in order to prevent or minimize the transmission of pathogens.[5] Universal Precautions should be followed by all health care providers. The World Health Organization and Center for Disease Control recommend that all skin lesions should be cleaned immediately and covered, gloves should be used when handling blood, and that participation should immediately stop if bleeding occurs. The athlete can return to play once the bleeding has stopped and the wound has been cleaned and covered. Most leagues will not permit participation if blood is on the uniform regardless of the source.

The 1992 survey showed that 80% of NCAA schools' athletic departments are familiar with Universal Precautions, 62% have education programs for their training staff and only one quarter of the schools post the Universal Precautions in their training rooms.

The effect of athletic participation on the HIV infected individual is also a concern. Magic Johnson originally retired from the NBA because his doctors believed that the stress of training and competing at the professional level may worsen the course of his infection. It is now believed that moderate exercise can cause an increase in immune system function.[2] Moderate exercise may cause a decrease in the occurrence of some cancers as well as cause an increase in endogenous opioids that can also protect immune function. Exercise and athletic participation reduces stress and anxiety. Some believe that stress and anxiety may open a window of opportunity for AIDS to develop. Athletic activity probably does not make HIV infection progress to AIDS. It may in fact delay the onset of AIDS. Individuals symptomatic with AIDS are usually unable to continue playing at a high level of intensity.

While the risk of contracting HIV during sport is a theoretical possibility, the likelihood of this occurring is extremely small. Therefore, there are no justifiable grounds for involuntary restriction of an HIV positive athlete. The physician should counsel the athlete about the risks of transmitting the infection and strongly encourage him or her to choose a low risk sport option. In all cases the athlete's right to confidentiality must be protected. Universal Precautions should be adhered to by all athletic and medical staff. All sources acknowledge that recommendations will have to be modified if the available information changes in such a way as to warrant new initiatives.

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INFECTIOUS SKIN MANIFESTATIONS OF HIV AND AIDS

By Noreen Ahmad, MEDS 2000

Human Immunodeficiency Virus (HIV) can result in many dermatologic disorders, some of which may be the presenting sign of the disease. Many of the cutaneous disorders that are HIV specific, but also some common dermatoses, can present atypically when an individual is infected with AIDS. Usually, skin conditions can be broadly divided into those that are of an infectious nature and those that are non-infectious.

Non-infectious conditions can be further divided into neoplastic cutaneous lesions and various eruptions such as psoriasis, seborrheic dermatitis, Reiter's syndrome, eczema and other dermatoses.

Infectious conditions are the major cause of death in patients with AIDS.[2] These may also be divided into several categories. These conditions, and the presentation of some of the more commonly seen infections, will be concentrated on in the following discussion.

In an individual who is HIV positive, very few T-cells in the circulation actually harbour HIV(about 1 in 1,000-10,000); however, a much higher percentage of T-cells (about 1 in 10) and other cells in the lymph nodes are HIV infected.[2] This leads to destruction of CD4+ T-cells, reduction in their formation, and loss of their normal functions.[2] Therefore, in individuals who are infected with HIV, infections of the skin by agents that would normally cause only a minimal eruption, will proliferate and thrive because of the lack of normal numbers of CD4 helper T-lymphocytes.[1] The steady drop in the CD4 counts of HIV patients causes multiple interrelated malfunctions of both the humoral and the cellular branches of the immune system.[3] The infectious skin manifestations that may occur fall largely under three headings: Bacterial, Viral, and Fungal and Yeast. Physicians should be aware of specific eruptions of HIV, as well as of the increase in incidence of some more common dermatologic conditions which may have an atypical presentation. Recognition of these may lead not only to a diagnosis but also to more timely treatment.

BACTERIAL INFECTIONS

Staphylococcus Aureus

The most common organism causing cutaneous and systemic infection is *S. Aureus*.[4] This is attributable (i) to the fact that the nares can be colonized by the organism (ii) to subsequent skin infections which are due to lack of normal immune defenses (iii) to the high frequency of eczematoid dermatoses, and (iv) the regularity of indwelling catheters in many of these patients.[1] *S. aureus* usually occurs in the form of impetigo, cellulitis or folliculitis.[5] Fortunately, therapy with appropriate antibiotics is usually curative.[1]

Syphilis

Syphilis seems to be on the rise in North America. The lesions usually develop in a similar manner to those in HIV negative persons, but may have an altered course.[1] The presence of ulcerating genital lesions is not only painful, but also eases the spread of HIV after exposure to an infected partner.[6] Treatment of syphilis may be difficult, and increased doses of drugs may be required.

VIRAL INFECTIONS

Herpes Simplex

This viral infection occurs in about 20% of AIDS patients, usually as an ulcer at the perianal or perioral mucocutaneous junction.[6] It may also present as a blistering or bullous disease, or resemble impetigo.[6] As defenses become impaired, herpes simplex becomes chronic. In the past, chronic Herpes simples virus was used as a marker for suspicion of underlying HIV. Most strains respond well to acyclovir, although resistant strains that require combination therapy have also been found.[7]

Varicella Zoster

This infection is normally more severe and widespread in HIV infected patients than is herpes simplex.[6] Cutaneous lesions occur due to a lack of suppression of latent infection of dorsal root ganglia by the virus. The virus becomes reactivated by depression of cell mediated immunity, and this allows the virus to move along a dermatome and cause an eruption of clustered vesicles on an erythematous base.[1] The possibility of systemic involvement must also be remembered in varicella zoster infected patients.[8] Treatment is usually acyclovir, or a combination of acyclovir with foscarnet and other drugs.[5]

FUNGAL AND YEAST INFECTIONS

Candidiasis

Oral candidasis is an important cutaneous manifestation of HIV disease, and is often used to

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diagnose AIDS in a person with no other cause of immunodeficiency.[1] Mucosal candidiasis occurs in most HIV infected persons during their illness, and can be persistent and may cause dysphagia.[7] Commonly it produces white pseudomembranous plaques on the mucosa.[9] Treatment is instituted when the lesions are symptomatic, and consists of good hygiene and topicals such as nystatin or systemic treatment with ketoconazole or fluconazole.[1]

DERMATOPHYTOSIS

Infection with dermatophytes occurs in about 20% of patients with HIV infection.[1] The infection is more severe than in non-immunosuppressed individuals. Well defined erythematous lesions with scaling are typical, although unusual presentations such as tinea faciale have also been reported.[1] Dermatophytosis is usually treated with ketoconazole given with a carbonated cola beverage for acidity. This is the more commonly used treatment since ketoconazole also eradicates candida. Topicals can also be used for localized infections.[1]

Many individuals with HIV will develop cutaneous manifestations of their disease. Skin changes may be the first signs to alert a physician to a diagnosis of HIV or AIDS. Changes in the skin can alert the doctor to further deterioration in the patient's immunocompetence. Knowledge of the numerous cutaneous disorders that exist in individuals with HIV/AIDS are of great importance in lessening morbidity, and prolonging life.

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Ω

UNDERSTANDING THE ROLE OF CHEMOKINE RECEPTORS IN HIV INFECTION

By Walter Mak, MEDS 2001

Shortly after the identification of HIV as the agent responsible for AIDS, researchers were able to demonstrate that the T-cell CD4 surface molecule served as a receptor for HIV. Subsequent work, however, showed that murine cells transfected with the human CD4 gene were not susceptible to virus entry, thus revealing that while CD4 was necessary for incorporation of the virus into host cells, it was not sufficient on its own.[1] More recent studies have identified chemokine receptors, namely fusin and CCR5, as co-receptors for the envelope glycoprotein (Env) of HIV.[1,2,3,4,5]

Seminal work by Fiorenza Cocchi and co-workers gave the first indication that chemokine receptors may be involved.[6] Culture supernatants containing an activated CD8+ T-cell clone were shown to inhibit HIV replication, as manifested by a decrease in HIV-1 p24 (an HIV structural protein) production in the supernatant. Cocchi isolated various proteins secreted by the T-cell clone and identified them, via direct sequencing of various peptide fragments derived from the secreted proteins, as the b-chemokines RANTES, MIP-1a and MIP-1b, which function in the body as chemoattractants for the body's leukocytes, which direct them to sites of infection. Treatment of the supernatants with antibodies to RANTES, MIP-1a and MIP-1b resulted in p24 levels comparable to those found in supernatants devoid of CD8+ lymphocytes, thus identifying these chemokines as HIV-suppressive factors. However, it was discovered that certain strains of HIV were not sensitive to this suppression. In particular, it was noted that those strains of HIV which preferentially infected CD4+ macrophages (macrophage-tropic strains) were susceptible to b-chemokine-mediated suppression whereas other strains of the virus, which preferentially infected transformed T-cells (T-tropic strains), were unaffected by these chemokines.[6] Because macrophage-tropic and T-tropic strains of HIV were thought to differ only in the Env portion of the HIV genome,[3] there was speculation that the observed HIV-suppressive effects of the b-chemokines came at the level of viral entry into the host cell.[1] That is, that b-chemokines interfered with fusion of the viral glycoprotein envelope with the host cell membrane.

Subsequent studies by Deng et al. showed that this indeed was the case. They employed a modified strain of HIV-1, known as a luciferase reporter virus, in which a frameshift mutation had been introduced into the Env gene. While the modified virus was fully capable of infecting cells, the mutated Env gene ensured that further replication of the virus would not be possible, thus allowing researchers to quantitatively assess HIV-1 entry into target cells by measuring luciferase activity in the cells following exposure to HIV. Using this assay system, Deng et al. demonstrated conclusively that RANTES, MIP-1a and MIP-1b inhibited infection of target T-cells by macrophage-tropic HIV, further implicating chemokine receptors in the HIV infection process. At this point it appeared likely that such receptors act as co-receptors for HIV.[1]

Several labs employed various methods to identify possible co-receptor candidates. In one approach, human embryonic kidney cells were co-transfected with CD4 and one of several b-chemokine receptors and then challenged with the HIV-1 based luciferase reporter virus described earlier.[1] It was discovered that cells transfected with CCR5 became susceptible to infection by macrophage-tropic HIV strains, which was not the case for cells transfected with any other chemokine receptor. Furthermore, cells transfected with only the CCR5 gene were resistant to infection, indicating a co-operative mediation of viral entry by both CCR5 and CD4. A separate study by Alkhatib et al. utilized cells expressing the lacZ gene of *Escherichia coli*. Cells containing the lacZ gene and expressing the HIV Env gene were mixed with murine cells co-transfected with CD4 and CCR5. The lacZ gene was integrated in such a way that fusion of the two cells would result in the production of b-galactosidase.[3] As predicted, fusion only occurred between Env-expressing cells and murine cells expressing both CD4 and CCR5. Similar fusion studies were extended by Dragic and co-workers, who were able to successfully block fusion between Env-expressing cells and cells containing CD4 and CCR5 by adding RANTES, MIP-1a and MIP-1b to the cell cultures. However, they found that if a certain amount of time elapsed before the chemokines were added to the culture, then fusion could not be blocked. This evidence, they thought, was suggestive of a competitive mechanism of inhibition of HIV.[2] The latter observation was presumably due to an overexpression of CCR5, which then negated the inhibitory effect of the chemokines. Thus, in the span of a few months, it was proven that CCR5 was the co-receptor for macrophage-tropic HIV.

Meanwhile, parallel studies sought to identify the co-receptor used by T-tropic HIV in gaining entry into host cells. Fusion experiments were performed where the CD4-expressing cells were transfected with a whole cDNA library derived from a human cell line.[4] Repeated subfractionation and screening allowed the investigators to

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isolate the co-receptor on a single 1.7 kb cDNA insert. This insert contained an open reading frame encoding a protein 352 amino acids in length. Analysis of the nucleotide sequence revealed that this protein was a member of the superfamily of G protein-coupled receptors with seven transmembrane segments, the same family to which all chemokine receptors belong. Termed 'fusin', this new protein was found to serve as a co-receptor for T-tropic HIV in much the same way that CCR5 mediated macrophage-tropic HIV infection. A stromal cell-derived chemokine was eventually identified as a ligand for this newly characterized co-receptor, and interestingly enough, it was also found to have an inhibitory effect on T-tropic HIV infection of T-cells.[7]

A puzzling observation that surfaced amidst all the work on AIDS in recent years was the observation that amongst cohorts of individuals with extensive exposure to HIV, there existed a tiny subset of persons who remained seronegative for the virus. Shortly after its discovery as an HIV co-receptor, investigators looked to determine if CCR5 would provide a clue. A team led by Michael Dean was able to map the CCR5 locus to chromosome 3p21.[8] Using complex molecular techniques, the CCR5 loci of more than 600 individuals from cohorts of various risk groups for AIDS were screened for genetic variants of the CCR5 gene. One such variant was detected in 10% of all screened individuals and was characterized by a 32-base pair deletion mutation, resulting in a receptor which lacked three transmembrane segments, including the region involved in G-protein coupling.[8,9] None of the individuals homozygous for the defective gene showed any obvious phenotype and all such individuals were seronegative for HIV despite having been exposed to the virus.[8, 9,10] No seropositive individuals were found to be homozygous for this deletion, suggesting that perhaps a defective CCR5 protein was responsible for conferring immunity to HIV. In a separate study, Liu and co-workers discovered two seronegative individuals who were both homozygous for the 32-base pair deletion and whose white blood cells were extremely resistant to macrophage-tropic HIV infection, and sought to investigate this immunity to HIV at the molecular level.[10] The gene encoding CCR5 in these two individuals was transfected into CD4-expressing cells and then assessed for ability to either fuse with Env-expressing cells, or permit infection by the luciferase reporter virus. The mutated CCR5 protein was capable of supporting neither cell fusion nor infection by HIV. To determine whether defective CCR5 was expressed at the cell surface, the gene was tagged with hemagglutinin prior to transfection. Subsequent probing of the transfected cells with fluorescing anti-hemagglutinin antibodies revealed that the defective molecule was not expressed at the cell surface. These findings provided the molecular basis for immunity of certain individuals to HIV. A point of interest was the finding that white blood cells from an HIV-resistant individual were shown to secrete ten times the normal amount of b-chemokines. This suggested another resistance mechanism, whereby an excessive amount of chemokines inhibits CCR5 binding to HIV Env, either by desensitizing the co-receptor through over-stimulation of the receptor or by competitive inhibition. More recent work has disproved the former possibility. Using pertussis toxin to arrest chemokine-mediated receptor signalling, researchers were still able to observe the same degree of HIV inhibition by the b-chemokines as that observed in earlier studies.[11]

Another point of interest was that while leukocytes derived from individuals homozygous for the 32-base pair deletion are known to be highly resistant to macrophage-tropic HIV, it had been shown that the same leukocytes were susceptible to T-tropic HIV infection.[2] This observation was explained by the theory that macrophage-tropic HIV is the dominant form of HIV in asymptomatic HIV-infected individuals.[9] Following initial infection, it is believed that the macrophage-tropic strain then evolves into a T-tropic strain of HIV.[12] This presumably correlates with the gradual loss of CD4+ T-cells and the onset of AIDS-related symptoms in the individual. Because the macrophage-tropic HIV cannot undergo replication in resistant individuals, the switch to a T-tropic strain never occurs and the individual remains uninfected. Support for this theory came with the discovery of a dual-tropic strain of HIV which has a demonstrated ability to use either CCR5 or fusin as a co-receptor.[12] This dual-tropic strain would take its place in the hypothesis as a transitory strain of HIV which would appear temporarily during the evolutionary process. Such speculative insights, however, await to be firmly proven or disproven.

With convincing evidence that fusin and CCR5 served as co-receptors for HIV in hand, researchers began to work out the specific details regarding the nature of the HIV-chemokine receptor interaction. Using various HIV chimeric constructs, researchers were able to ascribe susceptibility to chemokine-mediated inhibition of infection to the V3 loop domain of gp120.[11] Analogous studies involving chimeric constructs of the chemokine receptor itself has allowed investigators to further characterize the structural determinants of HIV-chemokine receptor binding.[13] Another area of related interest is the development of chemokine analogues as possible candidates for anti-viral therapy. One such analogue is a derivative of RANTES with a slight modification at the amino terminus.[14] This analogue, named aminooxypentane- or AOP-RANTES, has been shown to lack any chemotactic or leukocyte-activating activities while retaining a marked HIV-inhibitory effect.

While much of the work in this area of AIDS research is promising, one must be cautious as well. In recent months, several groups have claimed to identify other co-receptors for HIV and SIV, thus confounding the HIV infection story somewhat.[15] The presence of multiple co-receptors, each one ready to do HIV's bidding, would make the development of an effective anti-viral compound very difficult indeed. Nonetheless, in light of the considerable amount of progress made in the research of HIV co-receptors, there is reason to remain optimistic. The struggle towards a more complete understanding of HIV infection has, in the past two or three years, led us on a rapid and exciting journey of discovery. Uncovering the secrets of the HIV co-receptor and further characterization of its role in the entry of HIV into host cells has already begun, and will continue to yield valuable insights into the treatment and possible prevention of HIV infection.

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OCULAR MANIFESTATIONS OF AIDS

By Harpinder Paul Johar, MEDS 2000
and Marc Raymond, MEDS 98

Since its discovery almost 16 years ago, acquired immunodeficiency syndrome (AIDS) has quickly developed into a major public health concern worldwide. It represents the end-stage of a systemic infection triggered by Human Immunodeficiency Virus (HIV). This infection essentially cripples the immune system leaving the host prone to the development of multiple opportunistic infections and/or malignancies. Such complications have both shortened the life span of AIDS patients, and also severely affected the quality of what life they have left. With the advent of new measures to fight AIDS/HIV such as improved prophylaxis, antiretroviral drugs, and more effective treatment of opportunistic infections, the expected life span of AIDS patients has steadily risen. As a result, those AIDS-related complications which arise relatively late in the progression of AIDS are beginning to be seen at greater frequencies.[1] Ocular manifestations are an example of these "late-blooming" complications experiencing an increase in incidence due to the extended life expectancy of AIDS patients. Such ocular afflictions of AIDS were first noted by Holland et al. in 1982, and today it is estimated that over 70% of patients with AIDS will develop some sort of ocular manifestation, and 90% will have ocular disease at autopsy.[2] According to their respective etiology and course, these complications can be grouped into four main categories: microvascular disease, opportunistic infections, neoplasms, and neuro-ophthalmic manifestations. The purpose of this review is to provide the medical student with a brief, systematic overview of such manifestations and possible treatments. It is through effective diagnosis and management that vision loss can be circumvented, thus enhancing the quality of life for patients suffering from AIDS.

MICROVASCULAR DISEASE

Retinal microvasculopathy (RM) is the most common ocular manifestation of AIDS with between 40 - 60% of patients affected.[3] The hallmark of this disease process is the presence of cotton wool spots (CWS) on retinal examination (FIGURE 1). These appear as fluffy white lesions identical to those seen in hypertension, diabetes, and cytomegalovirus (CMV) retinitis (see later). They represent nerve fiber layer infarcts which arise due to focal occlusions of the retinal capillaries. In addition to cotton wool spots, RM may manifest itself as intraretinal hemorrhages, microaneurysms, and Roth spots (retinal hemorrhages with a white center).

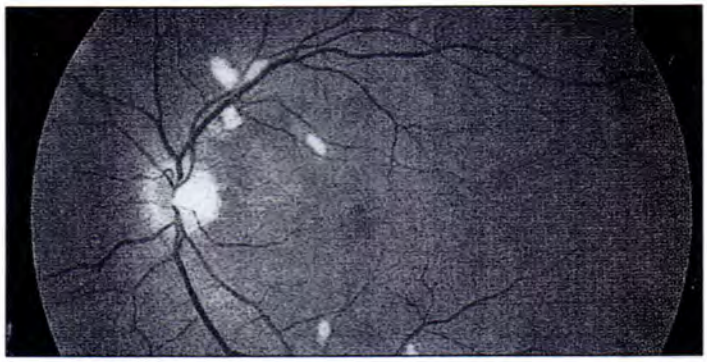

FIGURE 1. HIV retinopathy is characterized by the presence of multiple cotton wool spots.

The etiology of RM remains unknown. Some theories put forward to explain this phenomenon include microvascular occlusion due to either immunoglobin deposition or hyperviscosity. Alternatively, secondary swelling and microvascular obstruction due to HIV infection of endothelial cells may also be to blame.

It is important as clinicians to be able to distinguish between the cotton wool spots seen with RM and those seen with CMV retinitis. The main difference is that unlike CMV retinitis, the cotton wool spots due to microvasculopathy are not due to a direct infection of the retina. Therefore, RM cotton wool spots cause little alteration in vision and resolve spontaneously over a course of six to eight weeks without treatment. CMV retinitis, on the other hand, is best characterized as a progressive lesion which, if left untreated, invariably and very quickly causes blindness. The possibility of such differing results, stemming from the same initial symptom, conveys the importance in following up any AIDS patients presenting with cotton wool spots.

OPPORTUNISTIC INFECTIONS

Many organisms are able to take advantage of the immunocompromised state of AIDS patients and then manifest themselves in ocular lesions. They may be viral, bacterial, parasitic, or fungal.

VIRAL INFECTION

Herpes zoster ophthalmicus

Herpes zoster ophthalmicus (HZO) is a DNA virus that elicits a characteristic vesicular rash in the region of the ophthalmic division of the trigeminal nerve. Swollen eyelids, conjunctivitis, and keratitis (inflammation of the cornea) may also be associated with this disease. Although HZO is not considered an AIDS defining illness, it may be the initial sign of a HIV infection and any individual under the age of 50 who presents with HZO should be suspected of harboring HIV.[4] Treatment usually involves oral acyclovir, a synthetic purine nucleoside with selective activity against herpes virus infections.

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Cytomegalovirus

Cytomegalovirus (CMV) is another example of a virus capable of producing ocular lesions in AIDS patients. The lesion is commonly retinitis and is the most common intraocular infection associated with AIDS.[2] With more than 25% of AIDS patients succumbing to blindness due to CMV retinitis, it is also the leading cause of blindness within this sub-population.[5] CMV retinitis also tends to be a rather late manifestation of AIDS and hence survival after initial diagnosis is only 8-12 months.[6]

As mentioned earlier, the initial lesions of CMV retinitis appear as cotton wool spots on ophthalmoscopic exam. The difference between these CWS and those seen with retinal microvasculopathy is that these spread rapidly over a 1-2 week period to produce a retina characterized by white fluffy retinal necrosis with hemorrhages and vasculitis (FIGURE 2). These diseased portions of the retina have distinct borders which abruptly meet areas of normal retina. This may lead to retinal detachment further complicating the clinical picture for the patient.

Currently approved medications for CMV retinitis are gancyclovir and/or foscarnet. Since neither of these agents are able to eliminate the virus, treatment must be continued for the lifetime of the patient. Gancyclovir is a guanine analogue which inhibits viral DNA replication and forscarnet is a pyrophosphate analogue which inhibits CMV DNA polymerase. For maximum effectiveness, these drugs should be given at a high induction dose for 2-3 weeks, followed by a lower maintenance dose which is kept unless the retinitis flares up again.

Molluscum contagiosum

Molluscum contagiosum is caused by a DNA pox virus and commonly presents as raised eyelid lesions with umbilicated centers. It may also be associated with a chronic, low grade conjunctivitis. Treatment option involve excision, curettage, or cryotherapy. Given the immunocompromised state of AIDS patients, molluscum contagiosum tends to behave very aggressively leaving larger and more numerous lesions than usually seen in the endemic population.

BACTERIAL INFECTION

Syphilis

Syphilis is a chronic infectious disease caused by the bacterium Treponema pallidum. If left untreated, syphilis will gradually progress through primary, secondary, and tertiary stages of pathology, each of which may have ophthalmic manifestations. Primary syphilis may display chancre of the eyelids and conjunctiva. Secondary syphilis can exhibit a wide variety of complications including conjunctivitis, scleritis, interstitial keratitis, anterior uveitis, and papillitis (inflammation of the optic papilla). The third stage of this condition may display cranial nerve palsies, ptosis, optic atrophy, and for neurosyphilis, the Argyll Robertson pupil (pupil reacts to accommodation but not light).

A recent resurgence of syphilis in AIDS patients has been noted[7], and like other infectious agents, syphilis follows a more aggressive course in AIDS patients. High dose IV penicillin G has been found to be effective in the treatment of both syphilis and neurosyphilis.[7]

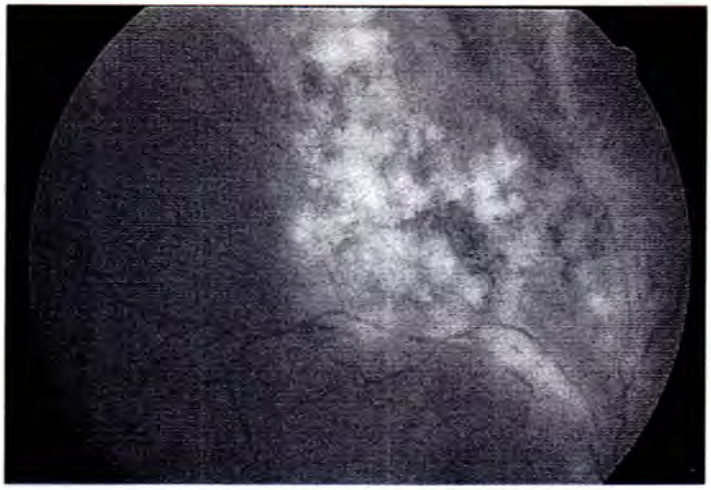

FIGURE 2. Typical features of CMV retinitis. The retinitis is characterized by a discrete, fluffy, white retinal necrosis, with retinal hemorrhages and vasculitis. There is a sharp, distinct border between the diseased and normal retina.

PARASITIC INFECTION

Ocular Toxoplasmosis

Toxoplasma gondii is a protozoan that commonly infects mammals and birds throughout the world. *T. gondii* infection in humans is usually asymptomatic, but in cases where the patient is in an immuno-compromised state such as AIDS, infection can be exceedingly progressive and fatal if left untreated. Ocular complications of such an infection include vitritis where the vitreous humor appears hazy. Retinal lesions may also be present and appear as white infiltrates which become pigmented scars when the initial inflammation subsides. *T. gondii* may also adversely affect the choroid.

Definitive diagnosis of toxoplasmosis in AIDS patients essentially relies on histological studies, isolating the parasite, and/or isolating *T. gondii* DNA from lesion sites. Drugs available to treat ocular toxoplasmosis are pyrimethamine, sulphadizine, and clindamycin.

Fungal Infection

Fungal complications are very common in AIDS, but ocular involvement is relatively rare. *Candida albicans* commonly infects the gastrointestinal tract of immunocompromised patients and may also afflict the eye. The typical *Candida* lesion consists of a fluffy white-yellow superficial retinal infiltrate. This may lead to the development of an overlying vitreous haze and ultimately vitritis. Treatment involves systemic therapy with amphotericin B.

NEOPLASMS

Kaposi's Sarcoma

Kaposi's sarcoma is a disease characterized by multiple vascular skin malignancies. It may present as a multifocal lesion with manifestations within the ocular adnexae (eyelids and orbit); or anterior segment (conjunctiva, cornea, iris) of the eye in addition to visceral involvement. Within the adnexae, flat or slightly-raised purple papules may be

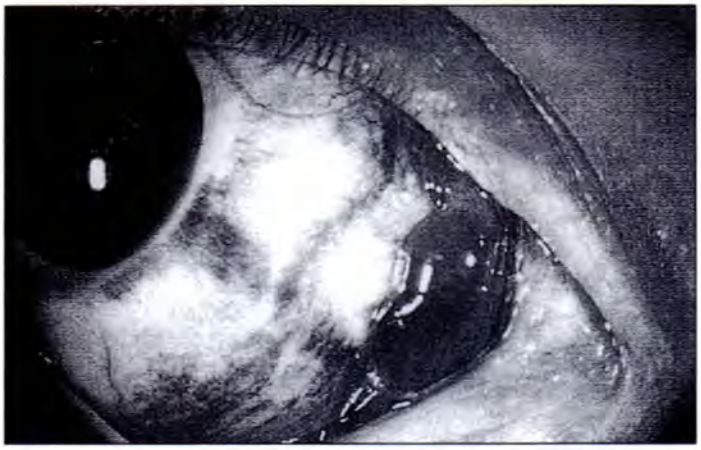

FIGURE 3. Kaposi's sarcoma of the conjunctiva resembles a subconjunctival hemorrhage.

visible on the eyelid. The orbit may also be involved, giving rise to proptosis (forward displacement of the eye) and double vision.

The effect of Kaposi's sarcoma on the anterior segment of the eye is usually limited to either the palpebral or bulbar conjunctiva. This commonly presents as a reddish plaque localized in the conjunctiva of the lower fornix (FIGURE 3) and may be misdiagnosed as a subconjunctival hemorrhage or a hemangioma.

Treatment of Kaposi's sarcoma involves excision of the lesion, use of chemotherapeutic agents such as vinca alkaloids, daunorubicin, and bleomycin, or radiation. If the Kaposi's sarcoma is multifocal, systemic chemotherapy may then be the only viable option.

NEURO-OPHTHALMIC MANIFESTATIONS

Over 39% of AIDS patients suffer from some form of intracranial disease.[7] This may arise from neoplasms such as non-Hodgkin's lymphoma or Kaposi's sarcoma, opportunistic infections causing encephalitis or meningitis, or cerebral abscesses. As a result of such lesions, patients may present with ocular manifestations of increased intracranial pressure and/or inflammatory or neoplastic neuropathy. Initially, these may include double vision or pupillary abnormalities. With time these may progress to more serious neuro-ophthalmic manifestations such as cranial nerve palsies, papilloedema, optic atrophy, gaze palsies, and visual field defects. Treatment of such neuro-ophthalmic manifestions largely depends on the correction of the initiating factor of the ocular alterations as well as symptomatic relief.

CONCLUSION

In summary, a multitude of distinctive ocular manifestations may appear in AIDS patients. The most common complication is retinal microvasculopathy, whereas opportunistic infections like CMV retinitis pose the greatest threat to vision. With the improved survival rates of AIDS patients, these ocular afflictions and other "late-blooming" AIDS complications will be seen at greater frequencies. It is important to recognize and treat these complications as our job in the treatment of AIDS is not only to extend the life of patients afflicted with AIDS but to also improve the quality of what life they have left.

ACKNOWLEDGMENT

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PrZITHROMAX*

(azithromycin dihydrate† / pfizer)

NAME OF DRUG

ZITHROMAX

(azithromycin dihydrate)

- Capsules 250 mg USP
- Tablets 250 mg
- Tablets 600 mg
- Powder for Oral Suspension 100 mg/5 mL and 200 mg/5 mL
- Single Dose 1g Packet

THERAPEUTIC CLASSIFICATION

Antibiotic

INDICATIONS AND CLINICAL USES

TREATMENT

ZITHROMAX (azithromycin dihydrate) is indicated for treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the following diseases and specific conditions. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

ADULTS

Upper Respiratory Tract

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes* (group A β-hemolytic streptococci) occuring in individuals who cannot use first-line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. **ZITHROMAX** is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of **ZITHROMAX** in the subsequent prevention of rheumatic fever are not available at present.

Lower Respiratory Tract

Acute bacterial exacerbations of chronic obstructive pulmonary diseases caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.* Community-acquired pneumonia caused by *S. pneumoniae, H. influenzae, Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in patients for whom oral therapy is appropriate.

Skin and Skin Structure

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus, S. pyogenes* or *Streptococcus agalactiae.*

Genitourinary Tract

Urethritis and cervicitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis.* Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established. Patients should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with **ZITHROMAX** may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be adjusted accordingly.

PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX (MAC) DISEASE

ZITHROMAX, taken at a dose of 1200 mg weekly, alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in persons with advanced HIV infections.

TREATMENT

CHILDREN (see **DOSAGE AND ADMINISTRATION; Use in Children, PRECAUTIONS** section)

Acute otitis media caused by *H. influenzae* (β-lactamase positive and negative strains), *M. catarrhalis* or *S. pneumoniae.* (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION** section.)

Pharyngitis and tonsillitis caused by *S. pyogenes* (group A β-hemolytic streptococci) occuring in individuals who cannot use first-line therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION** section.)

NOTE: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. **ZITHROMAX** is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of **ZITHROMAX** in the subsequent prevention of rheumatic fever are not available at present.

Community-acquired pneumonia caused by *H. influenzae, S. pneumoniae, M. pneumoniae* or *C. pneumoniae.* (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION** section.)

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness.

Safety and effectiveness for pneumonia due to *H. influenzae* and *S. pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

CONTRAINDICATIONS

ZITHROMAX (azithromycin dihydrate) is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or other macrolide antibacterial agents.

WARNINGS

Rare serious allergic reactions, including angioedema and anaphylaxis (with rare reports of fatalities) have been reported in patients on **ZITHROMAX (azithromycin dihydrate)** therapy (see **CONTRAINDICATIONS** section). Allergic reactions may occur during and soon after treatment with **ZITHROMAX.** Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *C. pneumoniae, H. influenzae, M. pneumoniae,* or *S. pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents including **ZITHROMAX** and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile.*

In the absence of data on the metabolism and pharmacokinetics in patients with lysosomal lipid storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease) the use of **ZITHROMAX** in these patients is not recommended.

PRECAUTIONS

General:

Since liver is the major route of elimination for **ZITHROMAX (azithromycin dihydrate),** the use of **ZITHROMAX** should be undertaken with caution in patients with significant hepatic disease.

No dose adjustment is needed in patients with mild renal impairment (creatinine clearance > 40 mL/min), but there are no data regarding **ZITHROMAX** usage in patients with more severe renal impairment. Thus caution should be exercised before prescribing **ZITHROMAX** in these patients.

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes,* in individuals with prolonged QT intervals. Although these adverse events have not been reported in clinical trials with azithromycin, one AIDS patient dosed at 750 mg to 1g daily experienced prolonged QT interval and *torsades de pointes.*

Use in Pregnancy:

Animal studies have demonstrated that azithromycin crosses the placenta. Safety of **ZITHROMAX** for use in human pregnancy has not been established.

Use in Nursing Mothers:

There are no data on secretion in breast milk. Safety of **ZITHROMAX** for use in human lactation has not been established.

Use in Children:

Acute Otitis Media or Community-Acquired Pneumonia: Safety and efficacy of **ZITHROMAX** in the treatment of children with acute otitis media or community-acquired pneumonia (dosage regimen: 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) under 6 months of age have not been established.

Pharyngitis and tonsillitis: Safety and efficacy of **ZITHROMAX** in the treatment of children with pharyngitis and tonsillitis (dosage regimen: 12 mg/kg on days 1-5) under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. Safety data with the use of ZITHROMAX at doses higher than proposed and for durations longer than recommended are limited to a small number of immunocompromised children who underwent chronic treatment.

In animal studies, treatment with azithromycin is associated with accumulation in various tissues, including the extra-cranial neural ganglia (i.e., retina and sympathetic nervous system). Tissue accumulation is both dose and time dependent, and is associated microscopically with the development of phospholipidosis (intra-lysosomal drug phospholipid complexes). The only evidence in animals that azithromycin is associated with alterations of intracellular phospholipid metabolism has been the documentation of small increases in phospholipid content after prolonged treatment (6 months) or exaggerated doses. Phospholipidosis has been observed at total cumulative doses only 2 multiples of the clinical dose. One month after withdrawal of treatment the concentration of azithromycin and the presence of phospholipidosis in tissue, including the retina, is at or near predose levels.

No data exist in humans in regard to the extent of accumulation, duration of exposure, metabolism or excretory mechanisms of azithromycin in neural tissue such as the retina and the cochlea.

Rare cases of hearing loss have been reported (see **ADVERSE REACTIONS** section).

No data are available on the metabolism and pharmacokinetics of azithromycin in children with lysosomal lipid storage diseases (see **WARNINGS** section).

Prevention of Disseminated *Mycobacterium Avium* Complex (MAC) Disease:

Safety and efficacy of **ZITHROMAX** for the prevention of MAC in children have not been established. Limited safety data are available for 24 children 5 months to 14 years of age (mean 4.6 years) who received **ZITHROMAX** for treatment of opportunistic infections. The mean duration of therapy was 186.7 days (range 13-710 days) at doses of < 5 to 20 mg/kg/day. Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. While none of these children prematurely discontinued treatment due to a side effect, one child discontinued due to a laboratory abnormality (eosinophilia). Based on available pediatric pharmacokinetic data, a dose of 20 mg/kg in children would provide drug exposure similar to the 1200 mg adult dose but with a higher C_{max}.

Use in Elderly:

The pharmacokinetics in elderly volunteers (age 65 to 85) were similar to those in younger volunteers (age 18 to 40) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for elderly patients with normal renal and hepatic function receiving treatment with this dosage regimen.

Drug Interactions

Antacids

Aluminum and magnesium containing antacids (Maalox®) reduce the peak serum levels but not the extent of azithromycin absorption. These drugs should not be taken simultaneously.

Cimetidine

Administration of cimetidine (800 mg) two hours prior to **ZITHROMAX** had no effect on azithromycin absorption.

Theophylline

Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. **ZITHROMAX** did not affect the pharmacokinetics of theophylline administered either as a single intravenous infusion or multiple oral doses at a recommended dose of 300 mg every 12 hours. There is one post-marketing report of supraventricular tachycardia associated with an elevated theophylline serum level that developed soon after initiation of treatment with **ZITHROMAX.** Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving **ZITHROMAX** and theophylline concomitantly.

Warfarin

ZITHROMAX did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with **ZITHROMAX** and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Zidovudine

Single 1g doses and multiple 1200 mg or 600 mg doses of **ZITHROMAX** did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of **ZITHROMAX** increased the concentrations of phosphorylated zidovudine in peripheral blood mononuclear cells.

Didanosine

Daily doses of 1200 mg **ZITHROMAX** had no effect on the pharmacokinetics of didanosine.

Rifabutin

Co-administration of **ZITHROMAX** and rifabutin did not affect the serum concentrations of either drug.

Carbamazepine
In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant **ZITHROMAX**.

Concomitant Therapy
The following drug interactions have not been reported in clinical trials with **ZITHROMAX** and no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. Nonetheless, they have been observed with macrolide products, and there have been rare spontaneously reported cases with **ZITHROMAX** and some of these drugs, in postmarketing experience. Until further data are developed regarding drug interactions, when **ZITHROMAX** and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy:

Digoxin: Elevation of digoxin levels.
Disopyramide: Increase in pharmacological effects.
Ergotamine or dihydroergotamine: Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Triazolam: Decreases in the clearance of triazolam and increases in the pharmacologic effect of triazolam.
Drugs metabolized by the cytochrome P450 system: Elevations of serum cyclosporine, hexobarbital, cisapride, and phenytoin levels.
Antihistamines: Prolongation of QT intervals, palpitations or cardiac arrhythmias with concomitant administration of astemizole or terfenadine.

No data are available on the concomitant clinical use of **ZITHROMAX** and gentamicin or other amphiphilic drugs which have been reported to alter intracellular lipid metabolism.

ADVERSE REACTIONS

TREATMENT
The majority of side effects observed in controlled clinical trials involving patients (adults and children) treated with **ZITHROMAX (azithromycin dihydrate)** were of a mild and transient nature. Approximately 0.7% of both adult patients (n=3812) and children (n=2878) who had multiple doses of **ZITHROMAX** discontinued therapy because of drug related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Potentially serious side effects including angioedema and cholestatic jaundice occured in less than 1% of patients.

Clinical:

Single 1-gram dose regimen (adults):
In adult patients (n=904), side effects that occurred on the single one-gram dosing regimen of **ZITHROMAX** with a frequency greater than 1% included diarrhea (6.1%), nausea (4.9%), abdominal pain (4.9%), vomiting (1.7%), vaginitis (1.3%), loose stools (1.2%), and dyspepsia (1.1%).

Single 2-gram dose regimen (adults):
Overall, the most common side effects in patients receiving a single 2-gram dose of **ZITHROMAX** were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18.2%), diarrhea/loose stools (13.8%), vomiting (6.7%), abdominal pain (6.7%), vaginitis (2.2%), dyspepsia (1.1%), and dizziness (1.3%). The majority of these complaints were mild in nature.

The following adverse experiences have been reported in patients under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods:

Allergic: arthralgia, edema, anaphylaxis (with rare reports of fatalities), serum sickness, urticaria, vasculitis;
Cardiovascular: cardiac arrythmias (including ventricular tachycardia), palpitations;
Gastrointestinal: anorexia, constipation, dehydration, dyspepsia, flatulence, pancreatitis, pseudomembranous colitis;
General: asthenia, paresthesia, muscle pain;
Genitourinary: interstitial nephritis, acute renal failure, nephrotic syndrome;
Liver/Biliary: abnormal liver function including drug-induced hepatitis and cholestatic jaundice, hepatic necrosis;
Nervous System: dizziness, headache, seizure, somnolence;
Skin/Appendages: serious skin reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis;
Special Senses: hearing disturbances including hearing loss, deafness and/or tinnitus, vertigo, reports of taste disturbance.

PREVENTION OF *MYCOBACTERIUM AVIUM* COMPLEX (MAC) DISEASE:
Chronic therapy with **ZITHROMAX** 1200 mg weekly regimen: The nature of side effects seen with the 1200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens.

Incidence[c] (%) of Treatment Related* Adverse Events** in HIV-Infected Patients Receiving Prophylaxis for Disseminated MAC

	Study 155		Study 174		
	Placebo (n=91)	Azithromycin 1200 mg weekly (n=89)	Azithromycin 1200 mg weekly (n=233)	Rifabutin 300 mg daily (n=236)	Azithromycin & Rifabutin (n=224)
Mean Duration of Therapy (days)	303.8	402.9	315	296.1	344.4
Discontinuation of Therapy (%)	2.3	8.2	13.5	15.9	22.7
AUTONOMIC NERVOUS SYSTEM					
Mouth Dry	0	0	0	3.0	2.7
CENTRAL NERVOUS SYSTEM					
Dizziness	0	1.1	3.9	1.7	0.4
Headache	0	0	3.0	5.5	4.5
GASTROINTESTINAL					
Diarrhea	15.4	52.8	50.2	19.1	50.9
Loose Stools	6.6	19.1	12.9	3.0	9.4
Abdominal Pain	6.6	27	32.2	12.3	31.7
Dyspepsia	1.1	9	4.7	1.7	1.8
Flatulence	4.4	9	10.7	5.1	5.8
Nausea	11	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	3.8	5.8
GENERAL					
Fever	1.1	0	2.1	4.2	4.9
Fatigue	0	2.2	3.9	2.1	3.1
Malaise	0	1.1	0.4	0	2.2
MUSCULOSKELETAL					
Arthralgia	0	0	3.0	4.2	7.1
PSYCHIATRIC					
Anorexia	1.1	0	2.1	2.1	3.1
SKIN & APPENDAGES					
Pruritus	3.3	0	3.9	3.4	7.6
Rash	3.2	3.4	8.1	9.4	11.1
Skin Discoloration	0	0	0	2.1	2.2
SPECIAL SENSES					
Tinnitus	4.4	3.4	0.9	1.3	0.9
Hearing Decreased	2.2	1.1	0.9	0.4	0
Taste Perversion	0	0	1.3	2.5	1.3

*Includes those events considered possibly or probably related to study drug
** >2% adverse event rates for any group
[c] Reflects the occurrence of ≥1 event during the entire treatment period

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In one of the studies, 86% of diarrheal episodes were mild to moderate in nature with discontinuation of therapy for this reason occurring in only 9/233 (3.8%) of patients.

PREVENTION OF *MYCOBACTERIUM AVIUM* COMPLEX (MAC) DISEASE:
In these immunocompromised patients with advanced HIV infection, it was sometimes necessary to assess laboratory abnormalities developing on study with additional criteria if baseline values were outside the normal range.

Prophylaxis Against Disseminated MAC
Abnormal Laboratory Values

		Study 155		Study 174		
Criteria*		Placebo	Azithromycin 1200 mg weekly	Azithromycin 1200 mg weekly	Rifabutin 300 mg daily	Azithromycin & Rifabutin
Number of Subjects[c]		(n=88)	(n=89)	(n=208)	(n=205)	(n=199)
Hemoglobin	< 0.8 x LLN[a]	31%	30%	19%	26%	21%
Platelet Count	< 0.75 x LLN	19%	16%	11%	10%	16%
WBC Count	< 0.75 x LLN	48%	49%	60%	53%	60%
Neutrophils	< 0.5 x LLN	16%	28%	23%	20%	29%
	< 500/mm³	6%	13%	5%	6%	8%
AST (SGOT)	> 2.0 x ULN[b]	28%	39%	33%	18%	30%
	> 200 U/L	10%	8%	8%	3%	6%
ALT (SGPT)	> 2.0 x ULN	24%	34%	31%	15%	27%
	> 250 U/L	2%	6%	8%	2%	6%

* secondary criteria also applied if baseline abnormal, as follows: Hemoglobin, 10% decrease; Platelet, 20% decrease; WBC count, 25% decrease; Neutrophils, 50% decrease; AST (SGOT), 50% increase; ALT (SGPT), 50% increase.
a lower limit of normal
b upper limit of normal
c number of subjects evaluable in any laboratory test is at least 98% of the total number of subjects

In a phase I drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (< 500 cells/mm³).

OVERDOSAGE

Symptoms:
There are no data on overdosage.

Treatment:
Gastric lavage and general supportive measures are indicated.
Up to 15 grams cumulative dose of **ZITHROMAX (azithromycin dihydrate)** over 10 days has been administered in clinical trials without apparent adverse effect.

DOSAGE AND ADMINISTRATION

TREATMENT

Adults:
CAPSULES: ZITHROMAX (azithromycin dihydrate) Capsules should be given as a single daily dose at least 1 hour before or 2 hours after a meal.
TABLETS: ZITHROMAX Tablets can be taken with or without food.
SINGLE DOSE 1 g PACKET: ZITHROMAX powder for oral suspension as Single Dose 1 g Packet can be taken with or without food after reconstitution.

Mixing Directions:
Directions for administration of the powder for oral suspension as a Single Dose Packet (1 g): The entire contents of the Packet should be mixed thoroughly with 60 mL (two ounces) of water. Drink the entire contents immediately, add an additional 60 mL (two ounces) of water, mix, and drink to assure complete consumption of dosage.
For skin and skin structure infections, upper and lower respiratory tract infections: The recommended dose of **ZITHROMAX** for the treatment of individuals 16 years of age and older is 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams.
Genitourinary: The recommended dose of **ZITHROMAX** for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid) and non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) oral dose of **ZITHROMAX**. This dose can be administered as four 250 mg capsules, four 250 mg tablets, or as one Single Dose Packet (1 g).
The recommended dose of **ZITHROMAX** for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is: a single 2 gram (2000 mg) dose of **ZITHROMAX**. This dose can be administered as eight 250 mg capsules, eight 250 mg tablets, or as two Single Dose Packets (1 g each).
For prevention of disseminated *Mycobacterium avium* complex (MAC) disease:
TABLETS: ZITHROMAX tablets may be taken without regard to food. The recommended dose of **ZITHROMAX** for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease is 1200 mg (two 600 mg tablets) taken once weekly. This dose of **ZITHROMAX** may be continued with the approved dosage regimen of rifabutin.
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of **ZITHROMAX** compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of **ZITHROMAX** should be undertaken with caution in patients with significant hepatic disease.

TREATMENT

Children:
POWDER FOR ORAL SUSPENSION: ZITHROMAX Powder for Oral Suspension should be given as a single daily dose at least 1 hour before or 2 hours after a meal.

Mixing Directions:
ZITHROMAX Powder for Oral Suspension:
Tap bottle to loosen powder. Add the directed volume of water. Shake well before each use. Oversized bottle provides shake space. Keep tightly closed. The table below indicates the volume of water to be used for reconstitution:

Amount of water to be added	Nominal volume after reconstitution (azithromycin content)	Azithromycin concentration after reconstitution
9 mL (300 mg bottle)	15 mL (300 mg bottle)	100 mg/5 mL
9 mL (600 mg bottle)	15 mL (600 mg bottle)	200 mg/5 mL
12 mL (900 mg bottle)	22.5 mL (900 mg bottle)	200 mg/5 mL

Acute Otitis Media or Community-Acquired Pneumonia:
The recommended dose of **ZITHROMAX** oral suspension for the treatment of children with acute otitis media or community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day), for a total dose of 30 mg/kg of **ZITHROMAX** (see chart below).

PEDIATRIC DOSAGE GUIDELINES FOR ACUTE OTITIS MEDIA OR COMMUNITY-ACQUIRED PNEUMONIA (Age 6 months and above) Based on Body Weight						
ACUTE OTITIS MEDIA OR COMMUNITY-ACQUIRED PNEUMONIA						
Dosing Calculated on 10 mg/kg on Day 1 dose, followed by 5 mg/kg on Days 2 to 5.						
Weight		100 mg/5 mL Suspension		200 mg/5 mL Suspension		Total mL per Treatment Course
Kg	lbs	Day 1	Days 2-5	Day 1	Days 2-5	
5	11	2.5 mL (1/2 tsp)	1.25 mL (1/4 tsp)			7.5 mL
10	22	5 mL (1 tsp)	2.5 mL (1/2 tsp)			15 mL
20	44			5 mL (1 tsp)	2.5 mL (1/2 tsp)	15 mL
30	66			7.5 mL (1 1/2 tsp)	3.75 mL (3/4 tsp)	22.5 mL
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL

Pharyngitis and Tonsillitis:
The recommended dose for children with pharyngitis and tonsillitis is 12 mg/kg once a day (not to exceed 500 mg/day) for 5 days for a total dose of 60 mg/kg of **ZITHROMAX** (see chart below).

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS AND TONSILLITIS (Age 2 years and above) Based on Body Weight			
PHARYNGITIS AND TONSILLITIS			
Dosing Calculated on 12 mg/kg once daily Days 1 to 5.			
Weight		200 mg/5 mL Suspension	Total mL per Treatment Course
Kg	lbs	Days 1-5	
8	18	2.5 mL (1/2 tsp)	12.5 mL
17	37	5 mL (1 tsp)	25 mL
25	55	7.5 mL (1 1/2 tsp)	37.5 mL
33	73	10 mL (2 tsp)	50 mL
40	88	12.5 mL (2 1/2 tsp)	62.5 mL

AVAILABILITY OF DOSAGE FORMS
CAPSULES: ZITHROMAX (azithromycin dihydrate) Capsules each contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The red, No. 0 hard gelatin capsules imprinted with "Pfizer" and **"ZITHROMAX"** in black ink, are packaged in white plastic (high density polyethylene) bottles of 30 and 100 or in a single treatment package (Z-PAK) of 6 blister packaged capsules per box.
TABLETS 250 mg: Each pink, film-coated, modified capsular-shaped **ZITHROMAX** tablet, engraved "Pfizer" on the upper face, and scored on the lower face, contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The tablets are packaged in white plastic (high density polyethylene) bottles of 30 and 100 or in a single treatment package (Z-PAK) of 6 blister packaged tablets per box.
600 mg: Tablets, engraved on front with "Pfizer", are white, modified capsular-shaped film-coated tablets containing azithromycin dihydrate equivalent to 600 mg azithromycin. These are packaged in HDPE bottles of 30 and 100 tablets.
POWDER FOR ORAL SUSPENSION: ZITHROMAX Powder for Oral Suspension, after reconstitution, contains a cherry flavoured suspension. Each bottle (high density polyethylene) provides azithromycin dihydrate equivalent to: 300 mg per 15 mL (100 mg/5 mL); 600 mg per 15 mL (200 mg/5 mL); 900 mg per 22.5 mL (200 mg/5 mL). Dropper is included in the package.
SINGLE DOSE 1 g PACKET: ZITHROMAX powder for oral suspension as a Single Dose 1 g Packet contains azithromycin dihydrate equivalent to 1000 mg of azithromycin in a sealed, laminated aluminum foil and polyethylene pouch.

Product Monograph available upon request.

† Product licensed from Pliva

Zithromax is a Schedule F drug.

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ONCE A DAY

CARDURA*

(doxazosin mesylate) BPH

Antihypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

INDICATIONS AND CLINICAL USE Hypertension: Treatment of mild to moderate essential hypertension, in a general treatment program in association with a thiazide diuretic and/or other antihypertensive agents, as needed for proper patient response. Doxazosin may be tried as a sole therapy in patients for whom treatment with other agents caused adverse effects or is inappropriate. **Benign Prostatic Hyperplasia (BPH):** Treatment of symptoms of benign prostatic hyperplasia (BPH). Onset of effect is rapid, with improvement in peak flow and symptoms seen within 1-2 weeks, and maintained over the entire study duration (up to 4 years). It may be used in hypertensive or normotensive BPH patients. A number of clinical conditions can mimic symptomatic BPH (i.e. stricture of urethra, stricture of bladder neck, urinary bladder stones, neurogenic bladder dysfunction secondary to diabetes, Parkinson's Disease, etc.). These conditions should therefore be ruled out before doxazosin therapy is initiated.

CONTRAINDICATIONS: Patients with a known sensitivity to doxazosin or quinazolines.

WARNINGS: Syncope and "First Dose" Effect: Doxazosin can cause marked hypotension, especially postural hypotension and syncope in association with the first dose or first few doses of therapy. A similar effect can occur if therapy is reinstated following interruption for more than a few doses. Postural effects are most likely to occur between 2-6 hours after dose. In controlled studies of doxazosin the incidence of syncopal episodes was 0.7%. Initial dose of 1 mg/day resulted in a 4% incidence of postural side effects with no cases of syncope. In controlled trials of normotensive BPH patients, the occurrence of syncope with doxazosin was 0.2%. In controlled trials in hypertensive BPH patients receiving doxazosin, the incidence of syncope was 0.8%. The likelihood of syncopal episodes or excessive hypotension can be minimized by limiting the initial dose of doxazosin to 1 mg, by increasing the dosage slowly and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Advise patients of the possibility of syncopal and orthostatic symptoms and to avoid driving or hazardous tasks for 24 hours after initial dose of doxazosin, after the dose is increased and after interruption of therapy when treatment is resumed. Caution patients to avoid situations where injury could result should syncope occur. If syncope occurs, place patient in the supine position. If this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of doxazosin. **Priapism:** Rarely (probably < 0.1%), $alpha_1$-antagonists such as doxazosin have been associated with priapism. This condition can lead to permanent impotence if not promptly treated. Advise patients of the seriousness of the condition.

PRECAUTIONS: General: Doxazosin therapy does not modify the natural history of benign prostatic hyperplasia (BPH). It does not retard or stop the progression of BPH, nor does it improve urine flow sufficiently to significantly reduce residual urine volume. However, significant reduction of mean residual volume has been shown in patients with baseline residual volumes > 50 mL. The patient may continue to be at risk of developing urinary retention and other BPH complications during doxazosin therapy. **Long-Term Safety and Efficacy:** The long-term safety and efficacy (i.e. > 4 years) has not yet been established in the treatment of benign prostatic hyperplasia. **Prostatic Cancer:** Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting doxazosin therapy to rule out the presence of carcinoma of the prostate. Doxazosin should not be used in patients with PSA > 10 ng/mL unless prostate cancer has been ruled out. **Orthostatic Hypotension:** While syncope is the most severe orthostatic effect of doxazosin (see WARNINGS), other symptoms of lowered blood pressure like dizziness, lightheadedness or vertigo can occur. They were common in clinical trials, occurring in up to 23% of all patients treated and causing therapy discontinuation in about 2%. In placebo-controlled titration trials the frequency of orthostatic effects in patients given 8 mg or more was 10%, compared to 5% at 1-4 mg, and 3% in the placebo-treated group.

In placebo controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was ≤ 1%. With maintenance doses of up to 8 mg/day in normotensive BPH patients, the mean decreases in sitting and standing blood pressure were small: 5/2 mmHg with doxazosin vs. 1/1 mmHg with placebo. Patients with occupations in which such events represent potential problems should be treated with particular caution. Advise patients of the need to lie down when symptoms of lowered blood pressure occur and to be careful when arising from a lying position. If dizziness, lightheadedness or palpitations are bothersome, they should be reported to the physician, and dose adjustment considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery. If hypotension occurs, place the patient in recumbent position and institute supportive measures as necessary. **Patients with Impaired Liver Function:** No information is available regarding use of doxazosin in patients with impaired liver function or in patients taking drugs known to affect hepatic metabolism. Doxazosin is extensively metabolized and excreted by the liver. Use in patients with impaired liver function is not recommended. **Patients with Impaired Renal Function:** Use in patients with impaired renal function requires careful monitoring. Clinical studies indicate that the disposition of doxazosin in patients with renal insufficiency is similar to that in patients with normal renal function, however accumulation of the drug with chronic dosing may occur. Less than 10% of the dose of doxazosin is excreted in urine as unchanged drug and metabolites. **Concomitant Conditions:** Doxazosin should not be prescribed to patients with symptomatic BPH who have the following concomitant conditions: Chronic urinary retention, high residual urine (over 200 mL), peak urine flow of 5 mL/sec or less, history of prior prostatic surgery, chronic fibrous or granulomatous prostatitis, urethral stricture, history of pelvic irradiation, presence of prostatic calculi, presence of large median lobe of prostate, presence of calculi in urinary bladder, recent history of epididymitis, gross hematuria, presence of neurogenic bladder dysfunction (diabetes mellitus, parkinsonism, uninhibited neurogenic bladder, etc.), hydronephrosis, presence of carcinoma of the prostate. Patients with recent history of myocardial infarction, transient ischemic attacks, or cerebrovascular accident within the past 6 months. **Pregnancy:** There are no studies in pregnant women. Doxazosin use not recommended in pregnant women unless the potential benefit outweighs the potential risk to mother and fetus. Doxazosin crosses the placental barrier. Studies in pregnant rabbits and rats at daily oral doses of up to 40 and 20 mg/kg respectively revealed no evidence of teratogenic effect. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival, an increase in embryo mortality and increases in fetal and placental weights. In peri-postnatal rat studies, postnatal development, at maternal doxazosin doses of 40 or 50 mg/kg/day, was delayed as evidenced by slower body weight gain and slightly later appearance of anatomical features and reflexes. **Lactation:** Studies in lactating rats indicate that doxazosin accumulates in rat breast milk. It is unknown whether this drug is excreted in human milk. Exercise caution when administering doxazosin to a nursing mother. In general, nursing should be interrupted. **Children:** Use of doxazosin is not recommended since safety and efficacy have not been established. **Elderly:** Use cautiously in elderly patients due to possibility of postural hypotension. An age-related trend towards increased incidences of postural hypotension and postural dizziness was seen in elderly hypertensive patients treated with this drug. **Peripheral Edema:** Fluid retention resulting in weight gain may occur during doxazosin therapy. In placebo-controlled monotherapy trials, patients receiving doxazosin gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo-treated patients. Overall incidence of body weight gain reported as a side effect in controlled trials was 0.8%. **Leukopenia/Neutropenia:** Analysis of hematologic data from patients receiving doxazosin in controlled trials showed that mean white blood cell (WBC) (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo. A data base search of 2,400 patients revealed 4 cases in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. No patients became symptomatic as a result of the low WBC or neutrophil counts. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% with doxazosin. **Cardiac Toxicity in Animals:** See Product Monograph. **Carcinogenesis, Mutagenesis and Impairment of Fertility:** See Product Monograph. **Drug Interactions:** Doxazosin is highly (98%) bound to plasma protein. *In vitro* data in human plasma indicate that doxazosin mesylate has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. Doxazosin has been administered to patients taking thiazide diuretics, beta-adrenergic blocking agents and non-steroidal anti-inflammatory drugs with no unexpected interactions reported. An additive hypotensive effect was observed when doxazosin was co-administered with thiazide diuretics and beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with ACE inhibitors or calcium channel blockers. *Digoxin:* Serum digoxin concentrations were not affected by treatment with doxazosin. *Cimetidine:* In a randomized, open-label, cross-over study in 22 male subjects, the single co-administration of 1 mg doxazosin with 400 mg b.i.d. cimetidine resulted in a 10% increase in mean AUC of doxazosin ($p = 0.006$), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The effect of further administration of cimetidine has not been studied.

ADVERSE REACTIONS: Hypertension: Doxazosin has been administered to approximately 4,000 patients in clinical trials of whom 1,679 patients were in controlled trials. The most serious adverse reaction occurring in controlled trials was syncope occurring in 0.7% of patients and resulting in a discontinuation rate of 0.2%. The most frequent adverse reactions in controlled clinical trials were: headache (16.5%), fatigue/malaise (14.8%), dizziness (14.6%), postural dizziness (8.7%) and edema (6.6%). Discontinuation of doxazosin due to adverse reactions occurred in 7% of patients. The following adverse reactions occurred with an incidence of ≥ 0.5% in the controlled clinical trials program (n=1,679): *Cardiovascular:* palpitation (3.6%); vertigo (3.0%); tachycardia (1.6%); postural hypotension (0.9%); arrhythmia (0.8%); syncope (0.7%). *Skin and Appendages:* rash (1.7%); pruritus (0.8%). *Musculoskeletal:* myalgia (1.3%); arthralgia (0.8%). *Nervous System:* somnolence (4.9%); sexual dysfunction (3.5%); dry mouth (3.4%); anxiety/nervousness (2.3%); insomnia (2.2%); paresthesia (1.7%); depression/apathy (1.6%); increased sweating (1.4%); hypoesthesia (1.6%); agitation (0.7%); flushing (0.7%); tremor (0.6%); paroniria (0.5%). *Special Senses:* vision/accommodation abnormality (2.4%); conjunctivitis/eye pain (1.2%); tinnitus (0.8%). *Gastrointestinal:* nausea (3.9%); diarrhea (2.9%); dyspepsia (2.1%); abdominal pain (1.6%); flatulence (1.4%); constipation (1.3%); vomiting (0.7%). *Respiratory:* dyspnea (3.9%); rhinitis (3.0%); epistaxis (0.8%); sinusitis (0.6%); bronchospasm/bronchitis (0.5%). *Urinary:* micturition frequency (1.2%); polyuria (1.0%); urinary incontinence (0.8%); urinary disorder (0.7%). *General Body:* chest pain (2.7%); asthenia (2.7%); muscle cramps (1.7%); pain (1.3%); face edema (0.8%); weight increase (0.8%); general edema (0.5%). *Hematology:* decreases in platelets (3.9%), white blood cell (2.4%), hematocrit (1.6%), hemoglobin (1.4%), neutrophil count (1.0%) (see PRECAUTIONS). The following adverse reactions were reported in at least 2 but < 0.5% of 1,679 patients who received doxazosin in the controlled trial program: *Cardiovascular System:* angina pectoris, peripheral ischemia, hypotension; *Nervous System:* paresis, twitching, migraine, amnesia, movement disorders, emotional lability, abnormal thinking, depersonalization, pallor, hypertonia, ataxia; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Special Senses:* taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence; *Respiratory System:* coughing, pharyngitis; *General Body System:* hot flushes, back pain, infection, fever/rigors, muscle weakness. In uncontrolled trials or post-marketing experience the following occurred with an incidence of <0.5%: myocardial infarction, cerebrovascular accident, confusion, impaired concentration, pallor, parosmia, earache, tinnitus, renal calculus, influenza-like symptoms, priapism and jaundice. No clinically relevant adverse effects were noted on serum potassium or glucose, uric acid, blood urea nitrogen or creatinine. Doxazosin has been associated with decreases in WBC count (see PRECAUTIONS). Isolated case of elevated liver transaminases have occurred. **Benign Prostatic Hyperplasia:** Doxazosin has been administered once daily to 665 both hypertensive and normotensive BPH patients in controlled trials. The most serious adverse reaction that occurred was syncope (0.5%). The most frequent adverse reactions in controlled trials were: dizziness (15.6%), headache (9.8%) and fatigue (8%). Discontinuation rate of doxazosin due to adverse reactions: 9%. The following adverse reactions occurred with an incidence of ≥ 0.5% in the controlled BPH trials (n=665 doxazosin patients): *Cardiovascular:* dizziness (15.6%); edema (2.7%); hypotension (1.7%); palpitation (1.2%); tachycardia (0.9%); angina (0.6%); syncope (0.5%); postural hypotension (0.3%). *Skin and Appendages:* increased sweating (1.1%); pruritus (0.5%); rash (0.5%). *Musculoskeletal:* myalgia (0.6%). *Central and Peripheral Nervous System:* headache (9.8%); paresthesia (0.6%). *Autonomic:* dry mouth (1.4%); flushing (0.6%). Special Senses: abnormal vision (1.4%); conjunctivitis (0.5%); tinnitus (0.5%). *Psychiatric:* somnolence (3.0%); insomnia (1.2%); anxiety (1.1%); decrease libido (0.8%); depression (0.6%); nervousness (0.5%). *Gastrointestinal:* diarrhea (2.3%); abdominal pain (2.3%); dyspepsia (1.8%); nausea (1.5%); flatulence (0.8%). *Respiratory:* dyspnea (2.6%); respiratory disorder (1.1%); rhinitis (0.8%); epistaxis (0.6%). *Reproductive Disorders:* impotence (1.1%). *Neoplasm:* carcinoma (0.5%). *Urinary:* urinary tract infection (1.2%); dysuria (0.5%). *General:* fatigue (8%); pain (2%); back pain (1.8%); chest pain (1.2%); asthenia (0.8%); influenza-like symptoms (0.8%); viral infection (0.6%); fever (0.5%); weight increase (0.5%); malaise (0.5%). Additional adverse reactions have been reported, but are, in general, not distinguishable from symptoms that may have occurred in the absence doxazosin exposure. The following adverse reactions were reported by < 0.5% of 665 patients who received doxazosin in controlled or open, short- or long-term clinical studies: *Cardiovascular System:* myocardial infarction, bradycardia, sudden death; *Autonomic Nervous System:* pallor; *Metabolic:* hyperglycemia, gout; *Hematopoietic:* lymphadenopathy; *Reproductive System:* prostatic disorder, ejaculation failure, epididymitis; *Skin Disorders:* dry skin, genital pruritus, urticaria, maculopapular rash, erythematous rash, aggravated psoriasis, eczema; *Central Nervous System:* hypoesthesia, hypertonia, leg cramps, confusion, speech disorder, ataxia; *Psychiatric:* abnormal thinking, depersonalization, paroniria, emotional lability, impaired concentration, amnesia; *Special Senses:* earache, taste perversion, eye pain, visual field defect, cataract; *Gastrointestinal System:* melena, constipation, vomiting, gingivitis, increased appetite; *Respiratory System:* coughing, bronchospasm, bronchitis, upper respiratory tract infection, sinusitis, pneumonia; *Urinary System:* urinary retention, micturition disorder, abnormal urine, renal pain, urinary incontinence, cystitis; *Musculoskeletal System:* arthritis, tendon disorder, arthralgia, hernia; *General Body System:* rigors, hot flushes, allergy, sepsis, fungal infection; *Platelet Bleeding and Clotting Disorder:* hematuria, subarachnoid hemorrhage. Data from long-term (up to 50 months), open BPH studies (n=450) indicate a higher rate of dizziness in younger hypertensive (27%) and normotensive (22%) patients, impotence in younger hypertensive (8%) patients, and discontinuation rates in patients due to adverse events (16.7%) compared to data from short-term placebo-controlled BPH studies (n=665). See Product Monograph for complete Adverse Reaction information.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: No data available regarding overdosage with doxazosin in humans. If administration of CARDURA leads to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should be used. Renal function should be monitored and supported as needed. As CARDURA is highly protein bound, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION: Dosage must be individualized. The absorption of CARDURA (doxazosin mesylate) is not affected by food. When doxazosin is being added to the existing antihypertensive therapy, monitor the patient carefully for the occurrence of hypotension. If a diuretic or other antihypertensive agent is being added to doxazosin regimen, doxazosin dose reduction and retitration with careful monitoring may be necessary. If doxazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen. **Hypertension – 1-16 mg Once Daily:** The initial dose of doxazosin in hypertensive patients is 1 mg given once daily and this dose should not be exceeded. This starting dose is intended to minimize postural hypotensive effects. The maximum blood pressure reduction normally occurs between 2-6 hours after a dose. The dose may be slowly increased to achieve the desired blood pressure response. Usual dose range: 1-8 mg once daily. Maximum recommended daily dose: 16 mg once daily. Doses greater than 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily, the frequency of postural effects is about 12% compared to 3% for placebo. **Benign Prostatic Hyperplasia – 1-8 mg Once Daily:** The initial dosage of doxazosin is 1 mg given once daily. Depending on individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose. Recommended titration interval: 1- 2 weeks. Blood pressure should be evaluated routinely. Doxazosin should be discontinued if the drug has been increased to maximum tolerated dose and improvement in urinary flowmetry is less than 25% or if doxazosin side effects are more bothersome than BPH symptoms or if the patient develops a urinary complication secondary to BPH while on doxazosin therapy.

Availability: White tablets containing doxazosin mesylate equivalent to 1, 2 or 4 mg of doxazosin. Supplied in opaque plastic (high density polyethylene) bottles of 100 tablets.

Full Product Monograph available on request.

REFERENCES: 1. CARDURA-1*, -2*, -4* Product Monograph, Astra Pharma Inc. **2.** Lepor H et al. Doxazosin for benign prostatic hyperplasia: Long-term efficacy and safety in hypertensive and normotensive patients. *J Urol* 1997;157:525-530. **3.** Fulton B et al. Doxazosin. An update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. *Drugs* 1995;49(2):295-320.

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ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

Norvasc*

(amlodipine besylate/pfizer)

Brief Prescribing Information
NORVASC
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY
NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE
Hypertension
NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.
NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.
Chronic Stable Angina
NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS
NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS
Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.
Outflow Obstruction (Aortic Stenosis)
NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).
Use in Patients with Impaired Hepatic Function
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).
Beta-blocker Withdrawal
NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS
Use in Patients with Congestive Heart Failure
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.
Hypotension
NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.
Peripheral Edema
Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
Use in Pregnancy
Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
Nursing Mothers
It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.
Use in Children
The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.
Use in Elderly
In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).
Interaction with Grapefruit Juice
Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.
Drug Interactions
As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.
Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.
Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.
Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.
Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:
- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin.**
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids
Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

ADVERSE REACTIONS
NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.
Hypertension
In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):
Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).
Angina
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):
Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapula, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.
Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.
Treatment
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.
Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).
Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS
Availability
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE
Store at 15-30°C. Protect from light.

REFERENCES:

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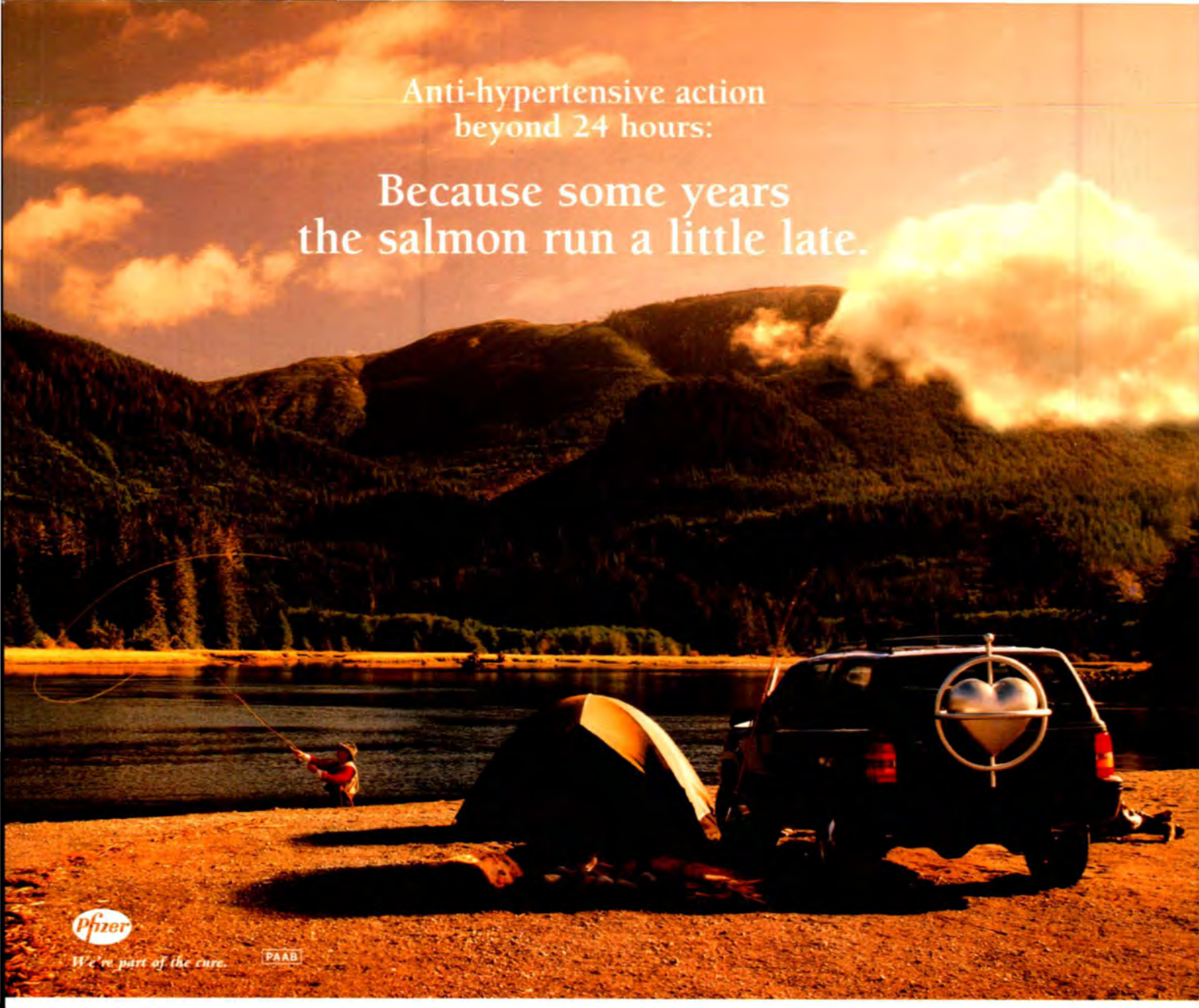


And in this morning's rush to get away from it all, he forgot his therapy at home.

He just became one of the 62% of Canadian hypertensives who regularly miss, forget or delay taking their medication (n=301).[7]

Of course, patients should be advised to take Norvasc* every 24 hours. But even a full 24 hours after a missed dose, long-acting[1,35,65] Norvasc* maintains blood levels which can deliver blood pressure reduction.[36-38,41,42,65]

With proven tolerability and, at 1.9%, an extremely low discontinuation rate.[1]

Once-a-day Norvasc*. Because the best things in life usually arrive in their own good time.

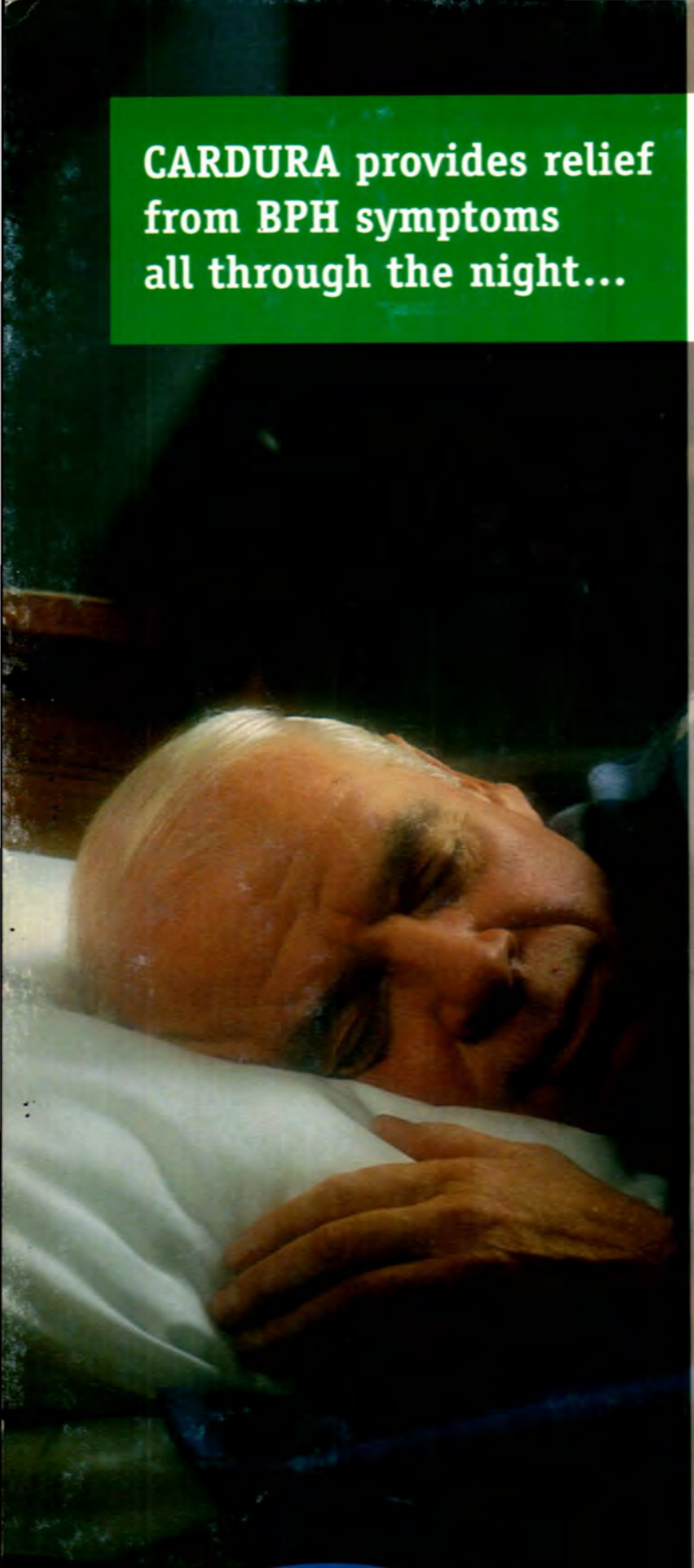
℗ Norvasc*
(amlodipine besylate/pfizer)

Allows extra time for human nature.

Norvasc* is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable. The most common adverse reactions include edema (8.9%) and headache (8.3%)[1]. For dosage adjustments in the elderly and hepatic impaired, consult the product monograph.

CARDURA provides relief from BPH symptoms all through the night...

and into the next day.



Continuous relief for a full 24 hours

- 22 hour half-life permits once-daily dosing which can be taken in the morning or the evening.[1]
- Rapid onset of relief with patient-assessed improvement observed within 1-2 weeks.[1]

Effective relief sustained over the long-term

- 4-year clinical trial establishes CARDURA with a documented record of long-term efficacy in the treatment of BPH.[2]
- No tolerance to the effect of CARDURA on urodynamics or BPH symptoms in patients treated over the long-term.[1†]

Proven tolerability helps patients continue with therapy[1]

- Smooth onset of action may help to minimize orthostatic hypotension.[3]
- Low incidence of orthostatic hypotension (0.3%) and impotence (1.1%).[1]

CARDURA is indicated in the treatment of symptoms of benign prostatic hyperplasia (BPH).

†The long-term safety and efficacy data for CARDURA treatment over 4 years has not yet been established.

**Pfizer Products Inc., used under license.

ONCE A DAY

CARDURA

(doxazosin mesylate)

BPH

Included on all provincial formularies (except P.E.I.)

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