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[American Red Cross "HIV/AIDS Update with Experts" 1/14/94]

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January 14, 1994

HIV/AIDS Update with the Experts

Agenda/Information

Thank you so much for being a part of this telecast! We're really looking forward to seeing you soon. Here's some information to help things run smoothly for you ....

American Red Cross contact: Susan Brown, 202-973-6028, fax: 202-973-6043.

Day of Jan. 14:

9:30 a.m. All panelists and those involved with telecast will meet at American Red Cross Frank Stanton Audiovisual Production Center; 5816 Seminary Road, Falls Church, VA 22041, telephone: 703-379-8160 (contact: Annie Mumgaard). 703 820.1533 Craig Reinertsm

At this time, we'll get to know each other better and run through the program. Then we'll move into the studio and do a run-through or two on the set. This way, everyone will get a better feel for how the program will flow. We'll then break for lunch. Then, panelists will go back onto the set and we'll be on the air at 2 p.m. eastern time, until 3:30 p.m.

Expenses: Please save ALL receipts for expenses incurred during your trip. The attached expense form, along with the receipts, needs to be sent by February 1 to Susan Brown: American Red Cross Office of HIV/AIDS Education, 1750 K. St. NW, Suite 700, Washington, DC 20006.

Conference Call Jan. 10:

Based upon all of your availability, I have scheduled the pre-telecast conference call for Jan. 10, 2:30-3:30 p.m. Eastern Time. During this time, we'll go over what the show will look like and panelists will have the opportunity to hear more about what their colleagues will be discussing and will be able to ask questions related to the telecast. If you will be at a telephone number other than the one at which you are normally reachable, please let me know by Jan. 6.

Publicity/Viewing:

The attached publicity flyer was sent to Red Cross local units as well as to state health departments, state education departments, and CDC-funded community based HIV/AIDS organizations. We expect that the telecast will be viewed by a range of people involved with HIV/AIDS education and services and that viewers will be watching in some 115 Red Cross sites as well as at the many colleges, universities, and medical facilities that can receive the program.

January 14 1993
HIV/AIDS Update with the Experts
Script/Outline
DRAFT

Please note: Mary Cotton, the moderator of the program, will be reading from telepromptor, as will Dr. Roger Dodd. All other panelists plan to speak extemporaneously ... you may wish to have notecards (light blue, not white ones) on your lap with key words if this is helpful.THESE CARDS WILL BE PROVIDED AT THE STUDIO THE DAY OF THE TELECONFERENCE, IF YOU WISH TO MAKE YOUR NOTES THEN.

MARY: Hello and welcome to "HIV/AIDS Update with the Experts", our fifteenth American Red Cross HIV/AIDS Forum Series telecast. I'm Mary Cotton, Director of the American Red Cross Office of HIV/AIDS Education, and your host today. Thank you for joining us.

Today we've gathered a group of distinguished scientists and leaders to provide us with an update on the state-of-the-art HIV/AIDS research and issues. This is an exciting opportunity for you in the viewing audience and our experts to discuss basic science, blood and biomedical issues, clinical aspects, and social policy considerations related to HIV/AIDS. I'm pleased to welcome Dr. Jay Levy, Professor of Medicine at the University of California, San Francisco. Jay is recognized as the co-discoverer of the AIDS virus and an expert in the study of long-term survivors. Also with us today is Dr. Roger Dodd, Head of the Transmissible Diseases Department, Holland Laboratory, American Red Cross ... someone who has been working in HIV/AIDS blood research since 1984. Roger will discuss issues and research related to HIV/AIDS and blood transfusion and related aspects. Also joining us is Dr. Harold Kessler, Associate Director of the Section of Infectious Disease at Rush Presbyterian Medical Center and Professor of Medicine and Immunology/Microbiology at Rush Medical College. He is well-recognized for his work in occupational transmission and an expert in the treatment of people with HIV/AIDS. National AIDS Policy Coordinator Ms. Kristine Gebbie also joins us today. Kristine's office is charged with coordinating national HIV/AIDS efforts.

As you can see, our panelists' areas of expertise cover quite a wide range of HIV/AIDS subjects. As we move through our presentations, please be sure to jot down your questions so when we open up the phone lines, you can call and ask our experts for their views.

Let's get going. Jay, you've done key research on basic science aspects of HIV and related topics, including long-term survivors. There have been media accounts lately of scientists saying that HIV is not the cause of AIDS. Jay, does HIV cause AIDS?

JAY AD LIB WITH GRAPHICS

- how HIV causes AIDS
- cellular response to HIV infection

- various strains of HIV
- how HIV suppresses immunity
- role of CD8+ and T-helper cells
- characteristics of long-term survivors
- effects of strong CD8+ response

(GRAPHICS DURING END PORTION OF PRESENTATION - from article)

MARY: Thanks Jay. It's very encouraging to hear how basic science research is making progress in unlocking the mystery of HIV and its assault on the immune system ... now I'd like to turn to Roger for a close-up look at HIV/AIDS and blood ... Roger, many HIV/AIDS educators are often asked questions relating to blood transfusions. The public is frequently frightened by media reports. Can you update us on the safety of the nation's blood supply and related issues?

ROGER READS FROM TELEPROMPTOR, NO GRAPHICS

- personal tragedy caused by HIV infection, regardless of how a person contracted the virus
- safety of national blood supply
- early ARC Blood Services efforts and how history of how screening process for HIV/AIDS has evolved
- current process of donor/donation screening
- HIV risk potential associated with gamma globulin, plasma, other blood products

MARY: Thanks Roger. That clarifies many of the questions we've ben asked related to the safety of our blood supply, and possibly has triggered other questions, which we'll invite from our viewing audience in a few moments. Moving on, Harold, you're working hard researching about HIV, as well as treating people living with HIV and AIDS, the clinical arena ... and you just published an article on occupational transmission of HIV in the Journal of the American Medical Association ... tell us more ....

HAROLD AD LIB.....

- occupational transmission/patient-to-patient transmission - putting risk in perspective
- what clinical practice related to HIV/AIDS looks like - experiences

• prophylaxis, treatment, and TB

• antiretroviral therapies - Concorde Study/consensus conference

MARY: Thanks Harold. So far, we've covered the scientific, biomedical and clinical aspects of HIV/AIDS ... now let's turn to Kristine. It's quite a time for us working in this field ... with your position as the key federal HIV/AIDS official, how about telling us what you see as the most pressing social policy concerns facing us today?

KRISTINE AD LIB WITH GRAPHICS

• priority social policy issues
(as appropriate, include availability of condoms in schools; health care reform; coordination of research)

• what NAPC's office is planning to do in relationship to these issues

MARY: Thanks Kristine. Quite a spectrum we've covered.

Now it's time to hear from you. Our telephone lines are open for your calls related to today's program ... the number is 1-800-237-0465. Please don't hesitate to phone in and take the opportunity to ask our distinguished guests questions ... especially those your audiences may have stumped you with!

PANEL AD LIB WHILE WAITING FOR CALLS

MARY (CLOSING): If you'd like to order a videotaped **(GRAPHIC)** copy of today's telecast, you can do so ONLY for the next five business days by calling the Red Cross General Supply Division at 1-800-969-8890, and asking for the January 14 HIV/AIDS Update with the Experts video. The cost is $15. Red Cross units are reminded that a copy of this telecast - as with all HIV/AIDS Forum telecasts - will be sent to each Statewide HIV/AIDS Network Coordinator.

Some news items: We are happy to announce a collaborative effort with the National Council of La Raza, one of the largest and most important national Hispanic organizations. Through this effort, La Raza's affiliates throughout the country will be encouraged to cooperate with their local Red Cross chapters in their efforts to expand HIV/AIDS education the Hispanic community. The Red Cross Hispanic HIV/AIDS training module will be the model for use by N-C-L-R and its affiliates.

(GRAPHIC) On February 9, from 2-3 p.m. eastern time, our next telecast "HIV/AIDS and the African American Church" will be coming your way and it's open to all. This will be an exciting interactive program. We'll feature religious leaders' perspectives on HIV/AIDS, and discuss the benefits of working together and the barriers we may need to overcome. We encourage Red Cross units to invite African American religious and

community leaders, neighborhood agencies and groups, such as Urban League, and state health and education department representatives, as appropriate, to view this live telecast. It will appear on two satellites, Ku-Band: GStar 2 (125 Degrees) on Transponder 8 (Horizontal--12157 MHz); and on C-Band: Galaxy 7 (91 Degrees) on Transponder 23 (Horizontal--4160 MHz).

(GRAPHIC) Our March 23 telecast will focus on Hispanic HIV/AIDS education. This made all the more exciting with our new collaboration with N-C-L-R. The telecast will be open to all who are interested. It will air from 2-3 p.m. eastern time. We'll be giving you more information on this in the near future.

For our non-Red Cross audience watching today, the programs I just mentioned will be widely available, both at about 115 Red Cross sites and many colleges, universities, and medical facilities. If you're interested in being part of those viewing audiences, or know of folks who may be interested, please contact your local Red Cross for more information.

To help us make these telecasts truly appropriate to your needs, we really need to hear from all of you tuning in about what you thought of today's telecast. Some of you have evaluation forms ... please fill them out and return them. If you don't have a form, we encourage you to write to us and mail or fax your comments, questions or suggestions about future telecasts. Here's our address and fax information. **(GRAPHIC)**Susan Brown, American Red Cross Office of HIV/AIDS Education, 1750 K. St Northwest, Suite 700, Washington, DC 20006. Fax: 202-973-6043. **(GRAPHIC)**For other questions, Susan Brown is your resource, at 202-973-6028.

A special thank you to our experts - Kristine, Harold, Roger, Jay. And thanks to everyone who joined in our viewing audience. Good day.

Anyone interested in and involved with HIV/AIDS should view ... *HIV/AIDS Update with the Experts* January 14, 1994

This satellite telecast - part of the Red Cross HIV/AIDS Forum series - will give viewers an HIV/AIDS update on:

♦ Basic Science ♦ Long-term Survivors ♦ Treatment
♦ Blood and Biomedical Issues ♦ Social Policy

Panelists

Kristine Gebbie, R.N., M.N.	National AIDS Policy Coordinator
Jay A. Levy, M.D.	Professor of Medicine, University of California, San Francisco
Peter A. Tomasulo, M.D.	Executive Vice President/Chief Operating Officer, American Red Cross Blood Services
Harold Kessler, M.D.	Associate Director, Section of Infectious Disease, Rush Presbyterian St. Luke's Medical Center; Professor of Medicine and Immunology/Microbiology, Rush Medical College

Moderated by:

Mary F. Cotton, Ph.D.	Director, American Red Cross Office of HIV/AIDS Education

Interactive phone-in session

Viewers can call to ask questions or to share experiences with the panel and with other viewers. The program will be transmitted live via satellite to downlink sites located in Red Cross chapters/blood regions nationwide as well as at alternate sites - the many colleges, universities, and medical facilities that have satellite receiving equipment.

Satellite Information

Date:	January 14, 1994
Program:	2-3:30 p.m. Eastern Time (Network test begins 1/2 hour prior to telecast)
Ku-Band:	GSTAR II (125 degrees) Transponder 8 (Horizontal) (12157 MHz) Audio: 6.2 & 6.8 MHz
C-Band:	Galaxy 7 (91 degrees) Transponder 15 (Horizontal) (4000 MHz) Audio: 6.2 & 6.8 MHz

*Videotapes of the telecast will be available for only five business days, following the program.
To order: contact the Red Cross General Supply Division - 1-800-969-8890.
Contact Susan Brown at (202) 973-6028, if there are any questions.

talking points.

T E L E F A X
American Red Cross
Office of HIV/AIDS Education
Washington, DC
Fax: (202) 973-6043

To: Steve Lee - (for forwarding to K. Gebbie)

Fax #: 202-632-1096

From: Susan M. Brown

Date: 1/5/94

Subject: January 14 Telecast Information

Total # of pages: 7

Hi Steve,
Here is the agenda, script/outline and publicity information I spoke of. Please share with Ms. Gebbie. You'll notice that Dr. Roger Dodd has replaced Dr. Peter Tomasulo (whose name is listed on the flyer) as the Red Cross Blood Services panelist. We're counting on each panelists presentation lasting about 10 minutes.

I'm looking forward to receiving your fax of Ms. Gebbie's talking points - as we discussed 1/3 - in the form of bullets by Thursday 1/6. The conference call operator will hook Ms. Gebbie in by phone around 2:30 on Jan. 10. Please don't hesitate to call me if you or Ms. Gebbie have any questions. Thanks for all your assistance.
(P.S. I didn't attach expense forms for obvious reasons as Ms. Gebbie's position is funded by a federal budget as is that of our program.)

KRISTINE M. GEBBIE
SCHEDULE FOR
JANUARY 14, 1994
(as of January 14, 1994)

FRIDAY, JANUARY 14, 1994
Washington.

7:30a Prepare paper "The Second Decade of HIV: Critical Issues for Nursing" for American Academy of Nursing HIV/AIDS Care Summit. (30m).

8:00a Meeting with Ken South, AIDS Interfaith Network. 750 office. (30m).

9:00a Meeting B. Moran and J. Messore on HIV guidelines in HP 2000. 750 office. (30m).

10:00a Meeting with C. Velez to discuss prevention policy. 750 office. (15m).

10:15a Staff car pick-up for travel to American Red Cross, 5816 Seminary Road (at Baileys Crossroads), Falls Church (703) 379-8160.

11:00a Meeting with other panelists of the American Red Cross "HIV/AIDS Update with the Experts" telecast to 116 sites. Topics panel discussion to cover social policy -- condoms in schools, research coordination, health care rform -- and an overview of the National AIDS Policy Office.

3:00p Staff car pick-up for travel to 750 office.

5:05p Depart Union Station on Amtrak #85 for Richmond. ($32).

7:05p Arrive Richmond.

MONDAY, JANUARY 17, 1994
Holiday.

5:00p Depart Richmond on Amtrak #96 for Washington.

7:00p Arrive Washington.

KRISTINE M. GEBBIE
SCHEDULE FOR
JANUARY 14, 1994
(as of January 14, 1994)

TUESDAY, JANUARY 18, 1994
Washington.

8:00a Staff car pick-up for travel to NIH, 9000 Rockville Pike, Building 31, Room 4C32, Bethesda.

8:30a Search Committee meeting for NIH Office of AIDS Research Director. (all day).

4:30p Staff car pick-up for travel to 750 office.

WEDNESDAY, JANUARY 19, 1994
Washington.
Agenda items for 1/24 Domestic Policy Council meeting due.

7:00a Prepare paper "The Second Decade of HIV: Critical Issues for Nursing" for American Academy of Nursing HIV/AIDS Care Summit. (2h).

12:30p Staff car pick-up for travel to 1518 K Street, N.W.

12:45p Informal discussion with National Alliance to End Homelessness Leadership Roundtable on ONAPC efforts to move HHS and HUD forward on homelessness among people living with HVB/AIDS. Staff present: Tim Fox. (1h).

1:45p Staff car pick-up for travel to 750 office.

2:30p Meeting with James Getty, chairman of the PLWA/HIV Committee to the D.C. Regional Planning Council to follow-up earlier meeting with D.C. activists. (15m).

3:00p Meeting with Jim Hall, Ambassador of Goodwill HIV/AIDS, Atlanta to discuss April AIDS walk and prevention among the African-American community in Atlanta. Staff present: C. Velez, J. Gurrola. (30m).

7:00p Dinner with Collen Conway-Welch, Dean of School of Nursing at Vanderbilt University.

THE WHITE HOUSE

WASHINGTON

Outline for
Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator
at
Red Cross Videoconference
January 14, 1994

National Policy on HIV/AIDS

Research

- Investigate models for innovative research projects that find a cure or vaccine.
- Implement the Office of AIDS Research reforms.
- Forge new linkages between federal research agencies.
- Work to maintain appropriate support for HIV/AIDS research in the federal budget.
- Ensure strong community participation in the development of federal research policies and plans.

Cure, vaccine, supportive Rx, behavior

Services everyone in care –

- ~~Monitor the administration of the~~ Ryan White Care Act.
- Increase the level of services available to communities most severely affected, including the Title I cities, children and rural areas.
- Ensure provision of essential primary care needs.
  - health reform

Prevention

- Continue to target activities that are most useful in preventing ~~HIV/AIDS.~~
- Encourage the delay of sexual activity among young people age ~~18-~~25, and for those who chose to become sexually active to use condoms consistently and correctly for every sexual act.
- Encourage greater local input in establishing priorities for prevention activities.

Difficult issues

- Denial that a problem exists
- Debate focuses on the wrong questions -- "condom distribution" vs. "comprehensive education"
- Structure of the research process
- Health care reform
  - Universal coverage with no pre-existing conditions that exclude people from coverage.
  - Preserve federal programs that support the care and treatment of people with HIV/AIDS as health care reform is phased in.
  - Prescription drug coverage.
  - Long term care and home care benefits.
  - Mental health and substance abuse coverage.

- essential providers, such as physicians specializing in HIV/AIDS included in all plans.
- Confidentiality safeguarded.
- Prevention and wellness key elements.

- Role of partnerships and communities.

Anyone interested in and involved with HIV/AIDS
should view ... *HIV/AIDS Update with the Experts*
January 14, 1994

This satellite telecast - part of the Red Cross HIV/AIDS Forum series - will give viewers an HIV/AIDS update on:

♦ **Basic Science** ♦ **Long-term Survivors** ♦ **Treatment**
♦ **Blood and Biomedical Issues** ♦ **Social Policy**

Panelists

Kristine Gebbie, R.N., M.N.	National AIDS Policy Coordinator
Jay A. Levy, M.D.	Professor of Medicine, University of California, San Francisco
Peter A. Tomasulo, M.D.	Executive Vice President/Chief Operating Officer, American Red Cross Blood Services
Harold Kessler, M.D.	Associate Director, Section of Infectious Disease, Rush Presbyterian St. Luke's Medical Center; Professor of Medicine and Immunology/Microbiology, Rush Medical College

Moderated by:

Mary F. Cotton, Ph.D.	Director, American Red Cross Office of HIV/AIDS Education

Interactive phone-in session

Viewers can call to ask questions or to share experiences with the panel and with other viewers. The program will be transmitted live via satellite to downlink sites located in Red Cross chapters/blood regions nationwide as well as at alternate sites - the many colleges, universities, and medical facilities that have satellite receiving equipment.

Satellite Information

Date: January 14, 1994

Program: 2-3:30 p.m. Eastern Time (Network test begins 1/2 hour prior to telecast)

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*Videotapes of the telecast will be available for only five business days, following the program.
To order: contact the Red Cross General Supply Division - 1-800-969-8890.
Contact Susan Brown at (202) 973-6028, if there are any questions.

American Red Cross

National Headquarters
Washington, DC 20006

September 20, 1993

Ms. Kristine Gebbie
National AIDS Policy Coordinator
Office of National AIDS Policy Coordination
Executive Office of the President
Washington, D.C. 20500

Dear Ms. Gebbie,

I am writing to you to invite you to participate in a national satellite telecast on January 14, 1994, which will be conducted from our studio in Falls Church, Virginia. The telecast will serve as a technical update for HIV/AIDS educators working at the community level. The focus will be on basic science, drugs and therapies, the safety of the nation's blood supply and social policy. We would like you to be the panelist to discuss social policy, providing the audience with an overview of the functions of your office and the critical policy issues your office hopes to address.

The satellite television medium provides the opportunity to reach thousands of community based organizations and allows for interaction with the viewing audience, who will phone in with questions to be fielded by the panelists. The audiences for Red Cross **HIV/AIDS Forum** telecasts typically include Red Cross units, AIDS Service Organizations, state and local health departments, local affiliates of national organizations, and community colleges. It would be a wonderful opportunity for people from the grass roots to get to meet you and to talk with you.

In addition to yourself, the other proposed panelists are: Dr. Jay Levy, San Francisco General Hospital, to provide information on long term survivors and basic science; Dr. Thomas Arrowsmith-Lowe, Food and Drug Administration, to discuss drugs and therapies; and a representative from American Red Cross Biomedical Services to discuss blood-related issues.

We need a response at your earliest convenience in order to provide the necessary advance publicity to the organizations participating in the telecast to allow them the time needed to make local arrrangements.

In the event that you cannot schedule January speaking engagements at this time, may we publicize the fact that you have been invited to speak? In addition, should your schedule not permit you to participate on camera, we could videotape your segment in advance. However, this option would not give you the opportunity to respond to the audience directly and to hear from audience members first-hand.

Thank you for your consideration. We hope that you can join us on January 14th. Please call if you have any questions. My telephone number is 202/973-6001.

Sincerely,

Mary F. Cotton

Mary F. Cotton, Ph.D.
Director
Office of HIV/AIDS Education

National Headquarters
Washington, DC 20006

MAILED AT
BALTIMORE, MD
DROP SHIPMENT
AUTHORIZATION 113

PRESORTED
FIRST CLASS

American Red Cross

Ms. Kristine Gebbie
National AIDS Policy Coordinator
Office of National AIDS Policy Coordination
Executive Office of the President
Washington, D.C. 20500

American Red Cross

National Headquarters
Washington, DC 20006

November 29, 1993

Steve Lee
Executive Assistant/Scheduler
AIDS Policy Office
750 17th St. NW
Suite 1060
Washington, DC 20503

Dear Mr. Lee,

We are delighted that Ms. Gebbie accepted our invitation to appear as a panelist on a live satellite telecast January 14, 1994. Many thanks for your assistance regarding this matter. I am writing to provide some important details related to Ms. Gebbie's participation.

HIV/AIDS Update with the Experts, a telecast with a panel presentation/discussion format, will give viewers an update on basic science; long-term survivors; treatment; blood and biomedical issues, and social policy. Mary F. Cotton, Ph.D., Director, American Red Cross Office of HIV/AIDS Education will serve as moderator. Confirmed panelists include Jay A. Levy, M.D., of the University of California, San Francisco, who will provide basic science and long-term survivor information; and a representative from American Red Cross Biomedical Services to address blood and biomedical issues. We are awaiting confirmation from the clinical representative. It is our understanding that Ms. Gebbie will discuss social policy and an overview of the functions of the AIDS Policy Office and some of the critical policy issues she plans for the office to address.

This telecast, the fifteenth in a series produced by the American Red Cross Office of HIV/AIDS Education, will air January 14, 1994 from 2-3:30 p.m. Eastern Time. Originating from Red Cross studios in Falls Church, VA, just outside Washington, DC, it will be transmitted live via satellite to 116 sites located in Red Cross chapters/blood regions nationwide as well as to the many colleges, universities, and medical facilities that have satellite receiving equipment.

As the telecast is being promoted to Red Cross units as well as to other HIV/AIDS and health organizations and agencies - many of whom have already expressed keen interest in the topic - it is our expectation that many people involved in HIV/AIDS prevention education, services, and care, will view. The telecast will include an interactive phone-in session in which viewers call to ask questions or to share experiences with the panel and with other viewers.

This would involve a one-day commitment on your part. The panelists, the director, and I will meet at the audiovisual studio at 9:30 the morning of the program to discuss the telecast. Then the panelists will move onto the set for a full run-through/technical rehearsal. Then we'll take break for lunch and go on the air from 2-3:30.

If you or Ms. Gebbie have any questions, I am your Red Cross contact person and I welcome your calls at 202-973-6028.

Sincerely,

Susan M. Brown
Office of HIV/AIDS
Education

sent via fax 1/14

THE WHITE HOUSE

WASHINGTON

Talking Points
for Graphics
Red Cross Video Conference
by
Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator

January 14, 1994

The national strategy against AIDS includes three critical components:

Research
Treatment
Prevention

EDITORIAL REVIEW

HIV pathogenesis and long-term survival

Jay A. Levy

AIDS 1993, **7**:1401–1410

Keywords: HIV heterogeneity, long-term survival, cytopathicity, apoptosis, cytokines, CD8+ cell antiviral activity, T helper (TH) cells.

Introduction

HIV infection, like other viral infections, has long-term survivors. These individuals, defined as living more than 8 years with HIV infection (some now more than 15 years), show no symptoms of infection, and several have normal CD4+ cell counts. Through studies of long-term survivors, we have gained a great deal of information about the various viral and immunologic features that appear to correlate with control of HIV infection. Understanding the parameters involved in HIV pathogenesis should help in directing antiviral therapies for all infected individuals.

Early steps in HIV infection

HIV is now known to consist of a heterogeneous group of viruses transmitted to hosts either by infectious particles or by virus-infected cells [1,2]. The virus-infected cell appears to be a major culprit in HIV transmission, both at the cellular and the mucosal level [3]. For example, direct infection of mucosal lining cells of the bowel has been demonstrated using *in situ* hybridization [4,5], and Phillips *et al.* have shown cell-to-cell transfer of HIV from lymphocytes or macrophages to mucosal cells in culture [6]. Given that up to 50–100 times more virus-infected cells than free virus can be found in body fluids [2,7], this means of transmission should be recognized. And vaccine development must consider the induction of appropriate immune responses for eliminating virus transfer by infected cells.

It has now been established that virus infection of the cell involves at least four receptors [2]: the CD4 molecule [8,9], galactosyl ceramide (Gal-C) on brain and bowel cells [10,11], and the Fc and complement receptors [12,13]; others may soon be identified. Fc and complement receptors can be involved in virus infection when HIV is complexed with antibody. These cell surface molecules permit infection of cells by the Fc portion of the antibody or by fixed complement via an antibody-dependent enhancement (ADE) process [2,12,13].

However, the interaction of the virus with cellular receptors alone is not sufficient for virus entry. Other steps that can involve conformational changes in the envelope and possibly cleavage of gp120 appear necessary to permit fusion of the viral envelope with a cell surface molecule [2]. The cellular site for this fusion remains to be defined. Moreover, recent studies have suggested that fusion alone may not bring the nucleocapsid into the cell to establish virus infection. Some HIV and simian immunodeficiency virus (SIV) strains attach and even show fusion at the cell surface but do not enter the cell [14,15]. Other processes appear to be required for the viral RNA to gain entrance into the cytoplasm.

Thus, the initial phases of virus infection can be summarized as three major steps: attachment, fusion and nucleocapsid entry, each depending on the virus and cell type involved (Fig. 1). It is important to study these three virus–cell interactions because each offers a direction for future antiviral approaches.

From the Cancer Research Institute and Department of Medicine, School of Medicine, University of California, San Francisco, California, USA.

Sponsorship: Supported by grant numbers RO1 AI29394, RO1 AI30350 and U01 AI26471 from the Naional Institutes of Health.

Note: This paper was presented in part at a plenary session at the IX International Conference on AIDS, Berlin, June 1993.

Requests for reprints to: Dr J.A. Levy, Cancer Research Institute, School of Medicine, University of California, San Francisco, CA 94143-0128, USA.

 ISSN 0269-9370

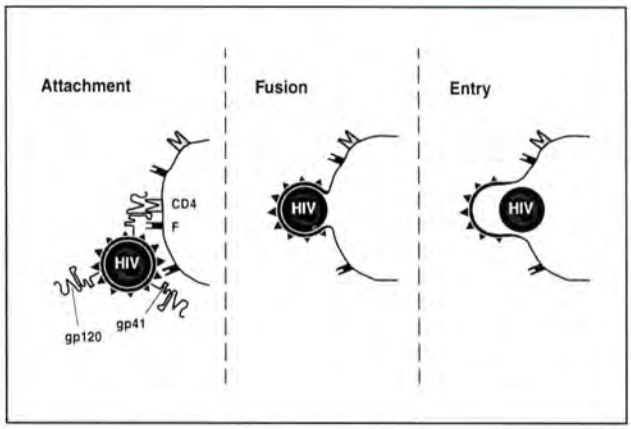

Fig. 1. HIV:cell entry. Three major steps involved in virus infection of cells. This concept is derived from recent observations in cell culture [2,14,15].

The initial site of HIV infection

Which cells are first infected after HIV transmission to the host is still not known. Obviously, if cell-to-cell transfer takes place, the mucosal lining of the bowel or uterine cavity could be the initial site of infection. Alternatively, lymphocytes or macrophages in these tissues, or in the cervix or urethra, could be infected by cell transmission or free virus. In the case of HIV entering the blood stream, infection would appear most likely to take place first in lymph nodes, where activated T cells and differentiated macrophages reside [2,16]. The resting T cells and undifferentiated monocytes found in the blood would not be susceptible to the virus during early stages [17–19]. Therefore, since very few activated lymphocytes and differentiated macrophages are usually present in the blood, relatively few circulating peripheral white cells, compared with lymphoid tissue cells, could be the initial site of HIV infection.

During this period of acute primary infection, high levels of HIV can be found in the blood, both as free virus [up to 5000 infectious particles (IP)/ml] and infected cells [20,21]. Within days to months, this level may decrease to very low quantities (for example, < 1 IP/ml) and can remain so for several months or years [2]. A rise in virus production then occurs concomitant with the onset of symptoms and eventually AIDS [2]. Basic questions on HIV pathogenesis revolve around the events that are associated with the initial control of virus replication during primary infection and around those processes that permit the reappearance of high levels of virus (see below).

Recent studies by Pantaleo *et al.* [22], Embretson *et al.* [23] and previously by Ràcz *et al.* [16] indicate that observations in the blood are reflected by findings in the lymph node. At various stages of infection, a large quantity of virus can be observed in the lymphoid tissue of infected individuals by polymerase chain reaction (PCR) and *in situ* DNA PCR techniques [22,23]. This virus load can be quite high compared with the apparently low quantities of virus in blood in asymptomatic individuals. Most importantly, however, Embretson *et al.* [23] found, using *in situ* RNA PCR, that while up to 30% of CD4+ lymphocytes in the lymphoid tissue can be infected by HIV, only about 1 in 400 of these cells are actually producing virus. Thus, during the relatively asymptomatic stage of infection, a mechanism is in place for controlling virus replication, not only in the blood (as noted above), but also in the lymph node.

It would therefore appear that during acute primary infection, and before the immune system of the host gains control of HIV, the early seeding of the virus to lymph nodes is responsible for the large virus quantity observed in these tissues during the subsequent persistent or asymptomatic periods. Viral replication then becomes suppressed by an active immune response. The nature of this response is considered below.

Heterogeneity of HIV strains

Once the virus enters a cell, the intracellular compartment can determine whether the virus replicates rapidly to high titer or slowly to low titer. This feature is related to cell type, as well as to virus strain [1,2,7]. When studied in peripheral white cells, these properties have led to a classification of rapid/high and slow/low viruses [24]. Moreover, HIV strains can differ substantially in their ability to kill cells by cell–cell fusion or single cell death. Some investigators refer to these viruses as syncytia-inducing [SI] and non-syncytia-inducing (NSI) viruses [25].

This known heterogeneity of HIV has been used by researchers to demonstrate certain viral phenotypes associated with infection of the brain, the bowel, and destruction of the immune system [26–29]. For example, concomitant with the development of disease is the emergence of an HIV variant that has changed from an initial, relatively non- cytopathic strain to one with properties of high virus production, increased cellular host range, and enhanced cytopathicity [28,29]. These findings suggest that HIV strains evolve within the host, possibly following selection by immune responses. They become variants that 'home out' in different tissues leading to pathologic sequelae, or have an increased capability of causing damage to the immune system. This change to a highly replicating pathogenic variant also reflects the rise in HIV production in the lymph nodes and peripheral blood of symptomatic patients [22,23,30–33].

The later HIV variant is related, but can be distinguished genetically from the initial, relatively non-

cytopathic strain. The major sites in the genome responsible for these biological differences reside in the highly variable envelope region (particularly the V1, V2, and V3 domains) [34–38] and the viral regulatory regions such as *tat* [39]. Only a few amino-acid changes can affect these biologic properties of HIV strains [34–39]. Thus, viruses undergoing relatively few mutations upon replication, can acquire new biologic as well as serologic features.

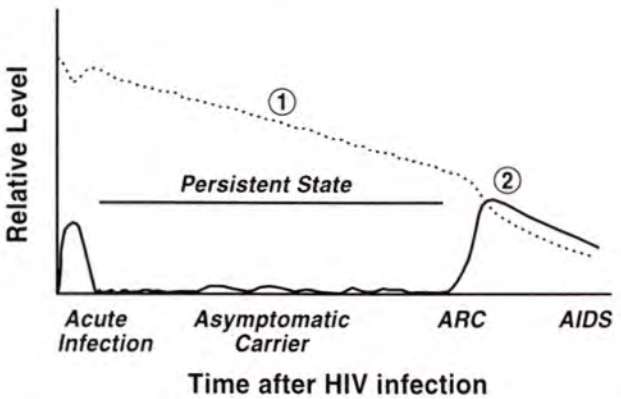

Fig. 2. Schematic diagram of events occurring after acute HIV infection. Prior to seroconversion, high levels of virus (——) can be detected in the blood. Subsequently, this viremia is reduced to low levels with episodic release of virus over time. Concurrent with the onset of clinical symptoms, a second high level of viremia occurs and remains raised throughout the terminal period. The CD4+ cell numbers (- - - - -) decrease during acute (primary) infection, then return to a level somewhat below normal. A slow decrease in CD4+ cell count, estimated to be approximately 60×10^6/l per year [42], occurs over time (phase 1). Subsequently, in some individuals developing disease, a marked decrease in CD4+ cell counts can be observed (phase 2) concomitant with the reemergence of high levels of viremia.

CD4+ cell loss

The suppressive mechanism preventing the emergence of the virulent, highly pathogenic strains must be determined (see below). Moreover, it is not clear what process over time causes the gradual deterioration of the immune system leading to a pathogenic course. This process, occurring generally when non-cytopathic strains are found in the blood, is reflected in part by the steady diminution in CD4+ cell function and number in the blood of HIV-infected individuals [2,40–42] (Fig. 2). As shown by the San Francisco Men's Health Study, infected individuals followed over time lose an average of 60×10^6/l CD4+ cells per year [42]. In some closely studied individuals, a dramatic reduction in CD4+ cells has been documented after a certain period of time, concomitant with development of clinical symptoms [2,40]. This enhanced loss in CD4+ cells appears to correlate with the emergence of more virulent cytopathic strains. In the latter case, a breakdown in the inhibition of virus replication appears to take place, permitting the replication of HIV to greater levels than previously evident in the infected host. Since each viral replicative cycle can give rise to as many as 10 mutations (albeit most of them lethal) [2,43], these changes could eventually produce the highly replicating variants that cause pathology in various tissues and damage to the immune system.

Effect of non-cytopathic HIV strains

In recent studies with Mosier *et al.* [44], we have identified a potential mechanism for the gradual loss of CD4+ cells over time. Severely immunologically compromised (SCID) mice, repopulated with human peripheral blood mononuclear cells (PBMC) and infected with viruses with different cell-killing properties as measured in cell culture, were used in these experiments (Table 1). The results indicated that infection with the relatively non-cytopathic macrophage-tropic HIV strains (for example, HIV-1_{SF162}) was associated with a faster depletion of CD4+ cells than infection with the highly cytopathic strains (for example, HIV-1_{SF33}) [44] (Fig. 3). Thus, an opposite result was observed in the animal compared with cell culture. The findings indicate the possible difficulties in directly relating *in vitro* observations to an *in vivo* situation.

Table 1. Biologic properties of HIV-1 isolates.

	Replication in		
HIV-1 strain	PBMC	MØ	Cytopathicity
SF162	++	++	–
SF33	++	±	+++
SF2	++	±	+

HIV-1 strains were tested for their ability to grow in peripheral blood mononuclear cells (PBMC), peripheral blood macrophages (MØ) and the induction of cytopathology in established T-cell lines or PBMC. + indicates the relative extent of these biological properties.

Most importantly, the results in this animal model system introduce a potentially new concept in HIV pathogenesis. They suggest that the relatively non-cytopathic strains, perhaps secondary to replication in macrophages, compromise the function of CD4+ cells and produce the gradual but persistent loss of these cells by means other than direct cell killing. For example, changes in the pattern of cytokines released by the HIV-infected macrophages could occur and reduce the level of CD4+ cells via programmed cell death or apoptosis (Fig. 4). Cytokines released from infected macrophages, such as tumor necrosis factor (TNF)-α are known to induce apop-

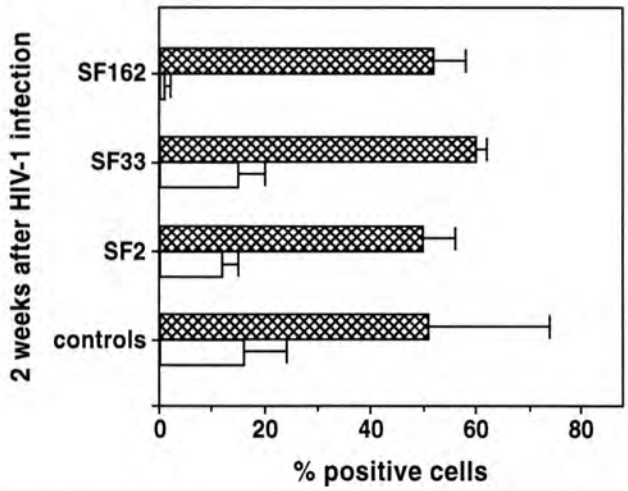

Fig. 3. Effect of HIV-1 infection on CD4+ and CD8+ cell number in SCID mice repopulated with human peripheral blood mononuclear cells. Note the marked reduction in CD4+ cells with the macrophage-tropic non-cytopathic HIV-1_{SF162} strain versus HIV-1_{SF33}, a highly cytopathic strain in cell culture. CD8+ cells (⊠); CD4+ cells (□). Data summarized from Mosier *et al.* [44].

tosis [45]. Moreover, loss of interleukin (IL)-1 production by the infected macrophages [46,47], particularly in the presence of antigen, can cause this programmed cell death [45]. These possibilities are under study.

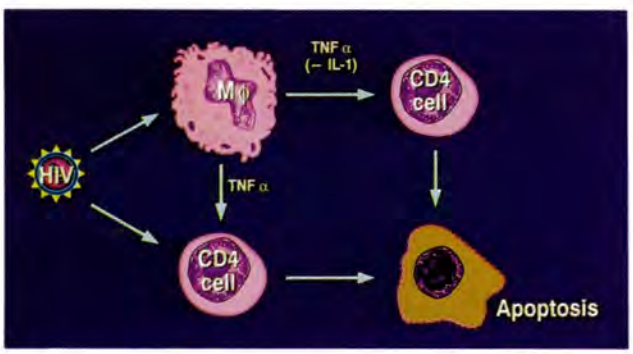

Fig. 4. Cell killing by non-cytopathic HIV-1 strains. Proposed mechanism for indirect loss of CD4+ cells. HIV-1 infection of macrophages can lead to the production of cytokines [e.g., tumor necrosis factor (TNF)-α] that can induce programmed cell death or apoptosis in CD4+ cells (infected or uninfected) [45]. Moreover, the loss of interleukin (IL)-1 production by infected macrophages [46,47] can cause apoptosis of CD4+ cells, particularly in the presence of antigen. In some cases, infection of CD4+ cells may increase this process of programmed cell death.

Two phases in HIV pathogenesis

The above observations suggest that when a sufficient loss of CD4+ cell function and number occurs by this indirect mechanism, the eventual emergence of the fast-replicating cytopathic strain can take place. Thus, a second phase of HIV infection occurs, characterized by the increased loss of CD4+ cells and frank disease (Fig. 2). A long asymptomatic period then would depend on the ability of the host's immune system to control the replication of even the relatively non-cytopathic strains, which, with time, appear to provide the venue for the emergence of the cytopathic variants. These two phases potentially involving HIV variants with different biologic properties could characterize the pathogenic course of infection, and thus each must be controlled by the host.

It is conceivable that the highly cytopathic strain, if introduced into the host during acute infection, might be more easily recognized and controlled by the host's immune system than the relatively non-cytopathic strain. Following the slow destruction of the immune system by a relatively non-cytopathic strain, the highly cytopathic variant might then re-emerge from a suppressed state. Alternatively, the cytopathic strain could be produced through multiple replicative cycles. Eventually, this virus would initiate the second phase of infection that leads to a rapid progression of disease. These possibilities require further study.

CD8+ cell response

The antiviral response of CD8+ T lymphocytes could be a major mechanism for control of HIV replication in PBMC in the host [48–52]. Present studies suggest that this anti-HIV activity is very important in delaying or preventing progression to disease [50]. The antiviral CD8+ cells, found at highest levels in asymptomatic individuals, suppress virus replication in cultured CD4+ lymphocytes and macrophages without killing the infected cells [48,50,51]. This anti-HIV suppressing activity of CD8+ cells, first described by Walker *et al.* [48], can be demonstrated in the laboratory by adding various concentrations of CD8+ cells to cultures of infected CD4+ cells. A low CD8+ cell/CD4+ cell ratio indicates a strong CD8+ cell response against the virus.

Table 2. Properties of the CD8+ cell antiviral suppressing activity.

Observed with activated CD8+CD28+ cells
Active against HIV-1, HIV-2 and SIV
Non-lytic mechanism
Major histocompatibility complex-unrestricted
Blocks HIV RNA expression
Does not block activation or proliferation of CD4+ cells
Mediated by a novel cellular factor

The characteristics of this CD8+ cell antiviral immune reaction are listed in Table 2. Most importantly, the process is not major histocompatibility complex (MHC)-restricted, can suppress the repli-

cation of all strains of HIV-1, HIV-2 and even SIV, and, as noted above, involves a non-cytotoxic mechanism [50–52]. The response does not correlate with CD8+ cell number and appears to be most evident with activated CD8+ cells with a CD28 phenotype [53]. This cell subset decreases with advancement to disease [53]. The same antiviral process is most probably occurring in lymphoid tissue where, as noted above, during the asymptomatic or persistent period, virus replication in infected cells occurs to only a limited extent [23]. The mechanism of virus suppression appears in part to involve a CD8+ cell antiviral factor (CAF) that differs from other previously described cytokines [54–56]. Its characteristics are listed in Table 3. The CD8+ cells block HIV transcription, suggesting that they arrest viral replication after integration [50].

Table 3. Characteristics of the CD8+ cell anti-HIV factor.

Produced only by activated CD8+ cells
Lacks identity to other known cytokines
Blocks HIV replication after virus integration
Active against HIV-1, HIV-2 and SIV
Small protein (< 30 kD)
Heat-stable
pH-stable
No effect on CD4+ cell activation or proliferation

Anti-HIV CD8+ cell response in high-risk seronegative individuals

In our early studies, the ability of CD8+ cells to inhibit acute HIV infection of lymphocytes in culture was observed only with CD8+ cells from HIV-infected individuals [50–52]. However, we have subsequently found that this activity can be demonstrated with CD8+ cells from some high-risk adult individuals who show no evidence of HIV infection either by PCR or antibody response (i.e., two out of five sexual partners of HIV-infected individuals), as well as with CD8+ cells from eight out of 24 uninfected children born to HIV-infected mothers. As a dramatic example, some years ago we studied monozygotic twins from Zambia followed by Drs S. Hira and P. Perrine. Only one twin was HIV-infected. The CD8+ cells from both twins have shown anti-HIV suppressing activity. Similar studies on cellular immune responses in uninfected infants and high-risk adults have recently been reported by Clerici *et al.* by showing cell proliferation to selective HIV peptides [57].

These data suggest that early strong cell-mediated anti-HIV response may have prevented the infection of these individuals before antibody production was initiated. However, it is also possible that these subjects were exposed to non-infectious virions or viral antigens, and infection was never established. Most importantly, all these observations support the evidence that cell-mediated and humoral immune responses occur separately, and that the cellular immune response can be a major determinant of HIV infection and its control. The processes responsible for maintaining this antiviral response remain to be defined.

Table 4. Subsets of CD4+ lymphocytes and their functions.

Subset	Cytokine produced	Function
TH1	IL-2 IFN-γ	↑ Cell-mediated immunity
TH2	IL-4 IL-10	↑ Antibody production

Cytokines produced by TH1 and TH2 subsets of CD4+ cells and their effect on the immune system. IL, interleukin; IFN, interferon.

T-helper cell subsets

Studies by Clerici and Shearer have suggested that specific subsets of CD4+ T-helper cells are instrumental in determining the extent of cell-mediated and humoral immune responses [58]. One T-helper cell subset (TH1) produces cytokines that increase cellular immunity, another (TH2) produces cytokines that enhance antibody production [58] (Table 4). To some extent, the interaction of the TH1 and TH2 cell subsets is competitive and overexpression of cytokines by one cell type can suppress the activity of the other (Fig. 5).

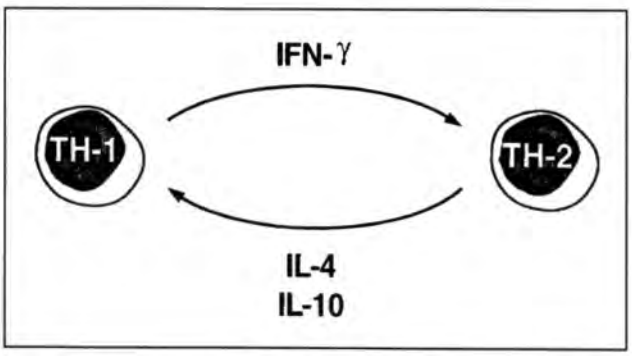

Fig. 5. Cross-regulation of the TH1 and TH2 subsets of CD4+ cells. The production of certain cytokines by TH1 and TH2 cells can suppress production of cytokines by the corresponding cell subset.

Based on these recent observations, a loss of cytokine production by TH1 cells, as documented over time by *in vitro* studies [58] (Fig. 6), could lead to the reduction of the cell-mediated immunity needed for continued suppression of HIV replication and spread in the host. A predominance of TH2 cells could be responsible for the decrease in TH1 activ-

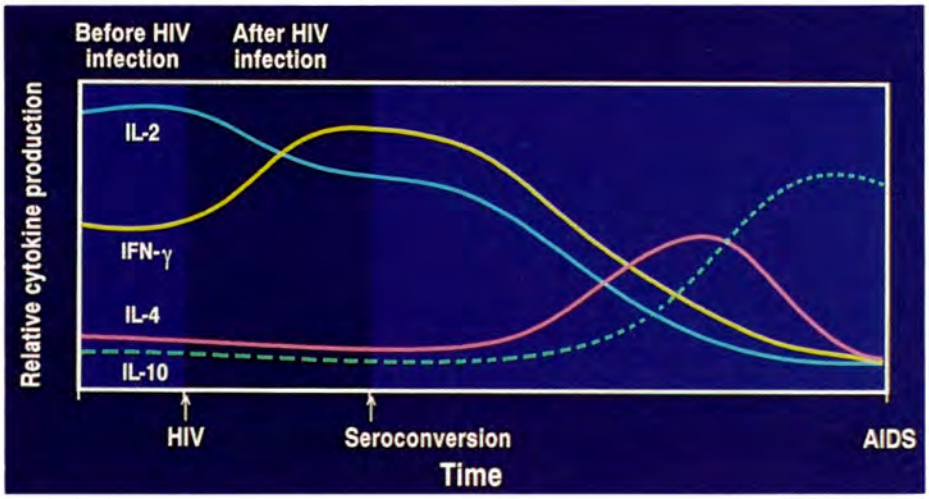

Fig. 6. CD4+ cell cytokine production before and after HIV infection. Studies of cultured CD4+ cells suggest that prior to HIV infection, the dominant T-helper (TH) cell subtype is TH1 with production of such cytokines as interleukin (IL)-2 and interferon (IFN)-γ. During the early stages of HIV infection, the TH1 subset predominates, but with advancement to disease it is replaced by a TH2 subset, reflected by the production of cytokines, IL-4 and IL-10. Data from Clerici and Shearer [58]. Modified from a figure from *Journal of NIH Research* with permission.

ity. It would be reflected by a high antibody production in the absence of a strong CD8+ cell response. What determine the switch from a predominant TH1 type response to the TH2 type response is an important question yet to be answered.

Features of long-term survival

Having discussed the recognized features of HIV pathogenesis — the heterogeneous viral strains, the emergence of cytopathic variants over time, and the role of immune responses — the nature of these parameters in long-term survivors is noteworthy (Table 5). First, as described initially, quantitative assays with PCR and measurement of infectious virus in PBMC and lymph nodes indicate that these individuals have a relatively low infectious virus load.

Table 5. Characteristics of long-term survivors.

Low infectious virus load
Infected with less cytopathic HIV strain
No enhancing antibodies
TH1 cell response is greater than TH2 cell response
Strong CD8+ cell antiviral response

Second, the virus that is found in these individuals shows properties of low cytopathicity or 'non-virulence'. These viruses do not replicate rapidly to high titer, may infect macrophages but do not grow in a wide variety of other cell types. They also do not readily kill lymphocytes or induce cell fusion in tissue culture. Based on the observations in the SCID-hu animal system [44], however, the replication of certain macrophage-tropic non-cytopathic strains could eventually lead to the loss of CD4+ cells by an indirect mechanism. Sufficient reduction in antiviral immune response could then result in the emergence of the cytopathic strains, and an accelerated decrease in CD4+ cells (Fig. 2).

Third, studies by our laboratory have shown that enhancing antibodies can be observed in individuals advancing to disease [59]. We have not found enhancing antibodies in long-term survivors.

Fourth, as discussed above, cytokine production by isolated CD4+ cells from individuals with an asymptomatic course suggests strongly that a TH1 cell phenotype is associated with an absence of disease and the predominant expression of TH2 cells occurs concomitant with symptomatic infection [58] (E. Barker and J. Levy, unpublished data). In essence, the maintenance of the TH1 cell profile appears to be a very important parameter ensuring host control of HIV infection.

Effect of strong CD8+ cell responses

All the above — low infectious virus load, non-virulent strains, lack of viruses sensitive to enhancing antibodies and maintenance of the TH1 response — can reflect the result of strong CD8+ cell antiviral activity in long-term survivors [60]. Replication of HIV and the resulting pathologic sequelae are blocked. Indeed, it was through our early studies of these subjects that this CD8+ cell activity was first defined, and more recently the novel antiviral factor associated with this response recognized.

For example, in long-term survivors as few as one CD8+ cell added to 20 CD4+ cells from infected individuals can control virus replication, whereas in AIDS patients large numbers of CD8+ cells are needed to control virus production by one CD4+ cell [60]. Moreover, results on some subjects over time suggest that a reduction in this CD8+ cell anti-HIV response is an early predictor of loss of CD4+ cells and progression to disease. In some infected individuals, a loss of CD8+ cell response can be documented before a reduction in CD4+ cell number [61] (Fig. 7).

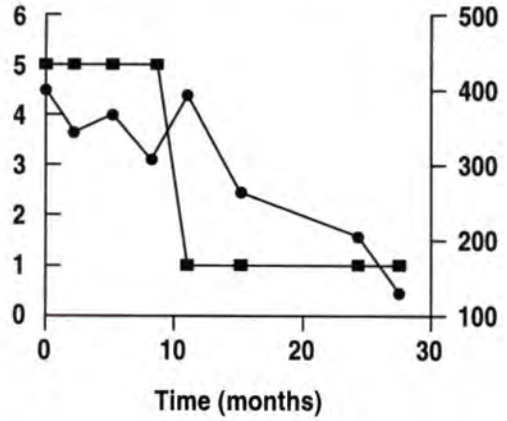

Fig. 7. CD8+ cell anti-HIV activity in an HIV-infected individual followed over time. In this subject, a loss of CD8+ cell response as reflected by the relative ability to suppress virus replication (y axis left; ■) decreases prior to a loss of CD4+ cell number $\times 10^6$/l (y axis right; ●).

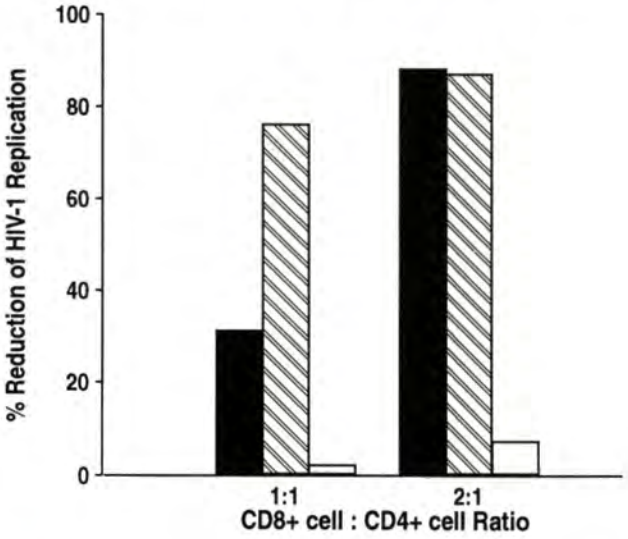

Fig. 8. Effect of cytokines interleukin (IL)-2 and IL-10 on the ability of CD8+ cells to suppress HIV replication. CD8+ cells from an infected individual were mixed with HIV-infected CD4+ cells at the input ratios indicated and cultured in the presence of suboptimal levels of IL-2 or IL-10. Some cultures received IL-10 and others received additional IL-2. The enhancing effects of IL-2, the TH1 cell cytokine, and the suppressing effects of IL-10, the TH2 cell cytokine, are evident. ■, control; ▨, IL-2 added; □, IL-10 added.

The reason for the decrease in CD8+ cell antiviral activity over time is not yet known. One mechanism could be the induction of apoptosis in these cells. This process occurring in CD8+ cells has been described previously by Meyaard *et al.* [62] and Gougeon *et al.* [63]. We have also confirmed that apoptosis takes place in these cells, as well as CD4+ cells (E. Barker and J. Levy, unpublished data). Most noteworthy, however, is the dramatic difference observed with CD4+ cells; apoptosis is much more frequent in CD4+ cells from progressors than with CD4+ cells from long-term survivors [62,63]. Their loss, particularly if of the TH1 subtype, could affect CD8+ cell antiviral activity (see below).

Another mechanism that we have recently uncovered may be more important in maintaining CD8+ cell activity. Since TH2 cells produce cytokines that can be inhibitory to TH1 cells, we investigated whether any of these cytokines might also indirectly or directly affect the antiviral activity of CD8+ cells. As shown in Fig. 8, IL-2 produced by TH1 cells increases CD8+ cell anti-HIV activity, whereas IL-10 produced by TH2 cells blocks this activity (C. Mackewicz and J. Levy, unpublished data). IL-10 also inhibits IL-2 production by TH1 cells [64]. Therefore, the transition of CD4+ cell subsets from TH1 to TH2, possibly reflecting a preferential loss of a TH1 cell type over time caused by HIV infection, leads to the production of cytokines such as IL-10 that block CD8+ cell activity. Moreover, IL-10 could cause a reduced release of cytokines, such as IL-2, that enhance this antiviral activity by CD8+ cells.

In summary, HIV pathogenesis and long-term survival appear to involve the steps listed in Table 6. Infectious viruses or virus-infected cells infect cells of the host by direct entry or cell-to-cell transfer. Specific cellular receptors are involved, but the mechanisms leading to final delivery of the viral nucleocapsid into the cell and the intracellular events deter-

Table 6. Steps involved in HIV infection and pathogenesis.

(1)	Acute virus infection with spread primarily to lymphoid tissues (and peripheral blood cells)
(2)	Virus attachment to cellular receptor, fusion and nucleocapsid entry into cells (Fig. 1)
(3)	Virus replication in cells (influence of intracellular factors)
(4)	Virus replication controlled by cellular immunity (CD8+ cell response) (Fig. 9)
(5)	Dominant TH1 cell responses enhance cell-mediated immunity
(6)	Gradual loss of CD4+ cell function and number (? role of non-cytopathic, macrophage-tropic HIV strains)
(7)	Switch from TH1 to TH2 cell subset responses (? role of HIV or cytokines)
(8)	Loss of CD8+ cell antiviral activity
(9)	Release of infectious virus and increased numbers of virus-infected cells (Fig. 10)
(10)	Enhanced virus replication leading to emergence of pathogenic strains (Fig. 2)
(11)	Further loss of CD4+ cells and function
(12)	Development of AIDS

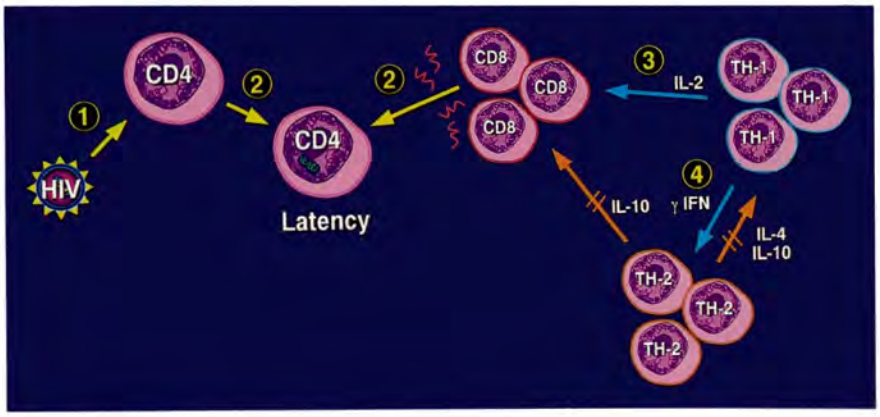

Fig. 9. Viral and immunologic events in persistent stage (long-term) survivors. HIV infection of CD4+ cells (step 1) is placed into a relatively latent state by the action of CD8+ cells and their antiviral factor (CAF) (step 2). This CD8+ cell anti-HIV response is increased through the production of cytokines secreted by TH1-type CD4+ cells (step 3). The TH1 cell cytokines also suppress the potential inhibitory effects of TH2 cell cytokines on this control of HIV infection (step 4).

mining virus replication are not yet defined. When a strong cellular immune response of CD8+ cells occurs, these virus-infected cells are placed into a state of relative cellular latency [2] (Fig. 9). While some virus escape can occur over time and a slow deterioration in CD4+ cell number and function can take place, long-term survival essentially depends on the maintenance of a persistent state characterized by a strong CD8+ cell anti-HIV response and low virus replication. This cellular immune activity mediated by the antiviral factor depends on the appropriate production of CD4+ cell TH1-type cytokines. Moreover, a lack of inhibition of both the CD8+ cell antiviral response and of TH1 cell activity by TH2 cell cytokines is required.

When the progressive stage begins, it can be characterized by a change from expression of the TH1 subtype of CD4+ cell to that of the TH2 subtype, with production of cytokines such as IL-10 that cause inhibition of the CD8+ cell anti-HIV response (Figs 8 and 10). This loss of CD8+ cell activity permits the emergence of virus from its latent state, and the release of infected cells and virus from the lymph nodes into the peripheral blood. These final events lead to the destruction of the immune system and the sequelae associated with development of AIDS. A delicate but flexible balance appears to exist between the maintenance of sufficient numbers of CD4+ cells (for example, TH1 cells) to sustain CD8+ cell anti-HIV activity and the presence of enough CD8+ cell antiviral response to maintain the levels of uninfected functioning CD4+ cells. Understanding what causes the collapse of this important interaction, through detrimental effects on either CD4+ cells or CD8+ cells, is the key to ensuring an asymptomatic state.

These features of HIV pathogenesis indicate that approaches that can maintain TH1 cell responses and/or CD8+ cell anti-HIV activity should keep the virus 'in check' and prevent its emergence into a virulent destructive strain (Fig. 11). Efforts directed at these cellular immune processes, as well as attention to the CD8+ cell antiviral factor, could bring long-term survival to all HIV-infected individuals.

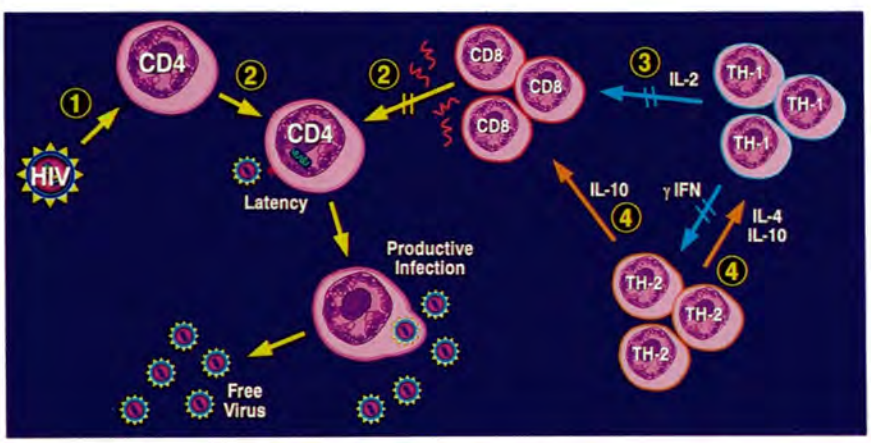

Fig. 10. Events occurring in individuals progressing to disease (Progressors). The events described in Fig. 9 are changed by a predominant expression of the TH2 versus the TH1 cell subtype. Cytokines such as interleukin (IL)-4 and IL-10 (step 4) can suppress cytokine production by TH1 cells and thereby affect the CD8+ cell antiviral activity. Moreover, IL-10 can directly suppress CD8+ cell antiviral responses (Fig. 8). The result of the loss of CD8+ cell antiviral activity is a release of HIV from latency and production of virus in lymph nodes and peripheral blood. These events lead to development of disease.

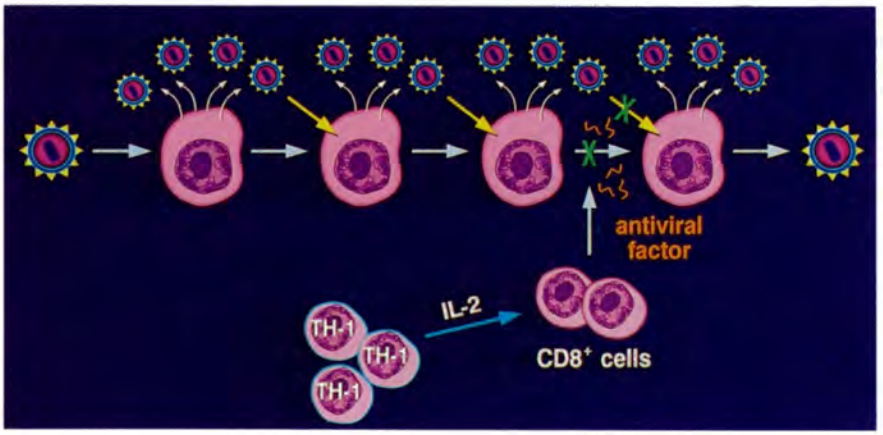

Fig. 11. Cellular immune responses and long-term survival. Approaches at controlling HIV pathogenesis. Methods directed at increasing CD8+ cell anti-HIV activity, the production of the CD8+ cell antiviral cytokine, or enhancement of TH1 cell responses would suppress HIV infection and maintain a long asymptomatic state.

Acknowledgements

The author would like to thank Ms Leslie Compere for excellent help in the graphics and Ms Ann Murai and Ms Christine Beglinger for help in preparation of the manuscript.

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THE WHITE HOUSE

WASHINGTON

November 22, 1993

Mary F. Cotton, Director
Office of HIV/AIDS Education
American Red Cross
National Headquarters
Washington, DC 20006

Dear Ms. Cotton:

Thank you for the invitation to attend the American Red Cross World AIDS Day Open House on Wednesday, December 1, 1993. Unfortunately, my schedule does not permit me to participate. I do, however, look forward to the January 14, 1994 teleconference.

Sincerely,

Kristine M. Gebbie, R.N., M.N.
National AIDS Policy Coordinator

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With best regards,
Jay Levy

MICROBIOLOGICAL REVIEWS, Mar. 1993, p. 183–289
0146-0749/93/010183-107$02.00/0

Vol. 57, No. 1

Pathogenesis of Human Immunodeficiency Virus Infection

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