Decision Analysis Example

Prophylaxis after Occupational Exposure to HIV

Human Immunodeficiency Virus Type 1 (HIV-1)

- CD4 receptor (coreceptors)
- Reverse transcriptase*
- Integrase
- RNA polymerase regulatory gene products
- Transport, assembly, and budding
- HIV aspartyl protease*

*Site of action for current drugs

HIV Infection after Needlestick Injury

- Direct inoculation into blood vessels
- Cutaneous dendritic (Langerhans) cells
- Delay from injury to infection
- Initial viremia (acute HIV syndrome)
- Chronic infection
HIV Infection after Needlestick Injury

Experimental models of HIV infection demonstrate the following sequence of events. After percutaneous or mucosal exposure to HIV, local replication of virus occurs in tissue macrophages or dendritic cells; host cytotoxic T cells will kill productively infected target cells. However, if infection cannot be contained at this stage, it is followed within 2 to 3 days by replication of HIV in regional lymph nodes; viremia then follows within 3 to 5 days of virus inoculation. Acceptance of this sequence of events carries significant implications. Given the rapid appearance of productively infected cells following the introduction of virus, regimens with the most rapid onset of activity, multiple sites of antiviral action, and greatest strength, such as HAART, are most effective.

HIV Infection after Needlestick Injury

- **Primary Infection is a Flu-Like Illness**
  - Experienced in 81% of HCWs
  - Occurred median 25 days after exposure
- **Seroconversion**
  - Median 46 days
  - By 6 months in 95% of HCWs
  - 3 persons at 6-12 months


Characteristics of HIV Disease in Donor Patients

- Mean time from infection to illness is about 10 years
- Plasma viremia
- Drug resistance
Questions

- What is the risk of infection after needlestick?
- What drugs are available for prophylaxis?
- How effective are they?
- What are their side effects?

HCWs with Occupational HIV Infection, June 2000

- 56 probable
- 138 possible

HCW Documented Seroconversions

HCWs with Percutaneous Blood Exposure

- CDC Prospective Cohort Study
  - Donor known to be HIV positive
  - HCW known to be HIV negative
  - 6 months of follow-up
  - 4 of 1,440 (0.0028) infected
- Combined with 22 smaller studies
  - 20 of 6,202 (0.0032) infected

Relative Risk of Seroconversion with Percutaneous Injury

Risk after Different Types of Percutaneous Blood Exposure

- CDC case-control study
- 31 cases had documented, occupational, percutaneous exposure to HIV-infected blood (needlestick or cut with scalpel or lancet), seroconversion temporally associated with exposure, and no other risk factors
- 679 controls had similar exposures and were seronegative at the time of exposure and 6 months later

**CDC Case-Control Study: 31 Cases, 679 Controls**

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* As opposed to superficial injury (scratch, no blood) or moderate injury (skin penetrated and blood appeared)

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**Risk Factors Not Found To Be Significant**

- Stage of HIV infection
- Type of device, including gauge of hollow needle
- Type of procedure, including whether the procedure was done as an emergency
- Use of gloves
- Time from device usage to exposure

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**Risk after Other Types of Exposure**

- Blood on mucous membranes
  - 1 case (0.0009)
- Blood on intact skin
  - No cases
- Exposure to other bodily fluids not visibly contaminated with blood
  - No cases
What Drugs Are Available for Prophylaxis?

- Nucleoside reverse transcriptase inhibitors
  - Requirement for phosphorylation
- Nonnucleoside reverse transcriptase inhibitors
- Protease inhibitors
- *Integrase inhibitors
- *Cell entry/fusion inhibitors

*Not currently recommended for prophylaxis

Adapted from: Walker B. IDSA 1998 Antiretroviral Therapy

Antiretroviral Therapy

- Nucleoside Analogues
- Non-Nucleoside Analogues
- Protease Inhibitors

Zidovudine (ZDV)

- Nucleoside reverse transcriptase inhibitor
- First drug approved for the treatment of HIV infection
- Decreased progression to AIDS in patients with CD4+ T-cell counts less than 500 per uL
- Resistance is frequent, especially after 6 months
Lamivudine (3TC)

- Nucleoside reverse transcriptase inhibitor
- Further decrease in progression to AIDS/death compared to zidovudine alone
- Licensed only for use with zidovudine
- Used alone, resistance is early and universal
- HIV strains that are resistant to lamivudine
- Are more susceptible to zidovudine
- Mutate less rapidly

Indinavir (IDV)

- Protease inhibitor
- Increase in CD4+ T-cell count and decrease in HIV RNA levels when given in combination with zidovudine and lamivudine
- Resistance occurs but requires over 10 amino acid substitutions

How Effective Are Drugs for Prophylaxis?

- Similar drugs work in studies of mice, cats, and nonhuman primates, but their efficacy is decreased by
  - Delaying drug initiation beyond 24 hours
  - Shortening drug use to less than 4 weeks
  - Decreasing daily drug dose
- Human studies
Case Reports of Zidovudine Failures

- 11 failures in HCWs
  - ZVD begun a median of 1.5 hrs after exposure
  - Median dose 1,000 mg/d
  - Median duration 21 days
- 5 additional failures in non-HCWs (large inoculum)
  - 1 blood transfusion
  - 1 suicidal self-inoculation
  - 1 assault on a prison guard with a needle-syringe
  - 2 intravenous exposures during procedures

Risk after Different Types of Percutaneous Blood Exposure

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<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine *</td>
<td>0.2</td>
<td>0.1 – 0.6</td>
</tr>
</tbody>
</table>

* 1000 mg/day for 3 to 4 weeks

HIV infection reduced by 79% (95% CI, 43 to 94%)
Percentage of HCWs with Zidovudine Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>236 using ZDV</th>
<th>439 without ZDV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea / vomiting</td>
<td>61</td>
<td>21</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Malaise / fatigue</td>
<td>33</td>
<td>7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Myalgia / arthralgia</td>
<td>10</td>
<td>6</td>
<td>&lt; 0.07</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8</td>
<td>1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Any side effects</td>
<td>75</td>
<td>26</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Other Side Effects

- Zidovudine
  - Anemia, neutropenia, abnormal LFTs

- Lamivudine
  - Nausea, abdominal pain, skin rash, pancreatitis

- Indinavir
  - Nausea, abdominal pain, hyperbilirubinemia, kidney stones

47 Surveillance Hospitals
June 1996 to November 2000

- 11,784 exposures to blood and bloody fluids
- When donor was HIV positive, 63% started post exposure prophylaxis
- 50% experienced adverse drug effects and 33% stopped drugs because of adverse effects
The Problem

- HIV infection leads to a terrible illness, and there are drugs that appear to provide protection after needlestick injury.
- Infection occurs only rarely after needlestick injury. Therefore, hundreds of people who will not get infected and thus cannot benefit from prophylaxis will have to be treated and experience drug side effects for every person whose HIV infection is prevented.
- How do we balance the possible benefits and risks and decide when prophylaxis should be used?

Steps in Decision Analysis

1. Imagine the model, and draw the tree
2. Identify the probabilities
3. Identify the outcome values
4. Calculate expected values
5. Perform sensitivity analyses

Types of Nodes

- Decision nodes (squares)
- Chance nodes (circles)
- Terminal nodes (branch endings)
Decision Tree 1

Choose

- No prophylaxis
- Prophylaxis

Rule 1

Node branches must be exhaustive and mutually exclusive.

Decision Tree 2

Choose

- No prophylaxis
  - HIV
- No HIV
  - Prophylaxis
Rule 2

At each chance node, the sum of the branch probabilities must equal one.
Steps in Decision Analysis

1. Imagine the model, and draw the tree
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Decision Tree 5

Choose

- Prophylaxis

Choose

- No prophylaxis
  - HIV
  - No HIV
  - 0.003
  - 0.997
  - Side effects
  - No side effects
  - 0.50
  - 0.50

Prophylaxis

Choose

- Zidovudine alone
  - HIV
  - No HIV
  - 0.0006
  - 0.9994
  - 0.000024
  - 0.999976
  - Side effects
  - No side effects
  - 0.50
  - 0.50

- Zidovudine + Lamivudine + Indinavir

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Proportion of health care workers infected after percutaneous exposure

- 0.0006 (0.005 x 0.2)

Proportion of HIV-infected patients with no detectable virus at 24 weeks

- 0.02
- 0.49

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Steps in Decision Analysis

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Possible Outcome Measures

- Percentage survival at 15 years
- Life expectancy
- Number of HIV infections avoided
- Cost of choices in dollars
- Utility
Rank and Scale Method for Measuring Utility

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rank</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis, no HIV</td>
<td>1</td>
<td>100.0</td>
</tr>
<tr>
<td>Prophylaxis, no side effects, no HIV</td>
<td>2</td>
<td>99.7</td>
</tr>
<tr>
<td>Prophylaxis, side effects, no HIV</td>
<td>3</td>
<td>99.0</td>
</tr>
<tr>
<td>No prophylaxis, HIV</td>
<td>4</td>
<td>8.6</td>
</tr>
<tr>
<td>Prophylaxis, no side effects, HIV</td>
<td>5</td>
<td>8.1</td>
</tr>
<tr>
<td>Prophylaxis, side effects, HIV</td>
<td>6</td>
<td>0.2</td>
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Steps in Decision Analysis

1. Imagine the model, and draw the tree
2. Identify the probabilities
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Two Methods

- Average out and fold back
- Path probability

Decision Tree 6

Choose

Prophylaxis

No prophylaxis

HIV

0.003

0.997

No HIV

Prophylaxis

Side effects

0.5

HIV

0.000024

0.999976

No HIV

No side effects

0.5

HIV

0.000024

0.999976

No HIV

Prophylaxis

Side effects

0.5

HIV

0.000024

0.999976

No HIV

No side effects

0.5

HIV

0.000024

0.999976

No HIV
Fold back "Side Effects" branch:
\[(0.000024 \times 0.2) + (0.999976 \times 99.0) = 98.9976288\]

Fold back "No Side Effects" branch:
\[(0.000024 \times 8.1) + (0.999976 \times 99.7) = 99.6978016\]

Fold back "Prophylaxis" branch:
\[(0.5 \times 98.9976288) + (0.5 \times 99.6978016) = 99.3477152\]
Decision Tree 7

Average Out and Fold Back

Average Out

\[(\text{Probability} \times \text{Outcome Value}) + (\text{Probability} \times \text{Outcome Value})\]

\[\text{Expected Value}\]

Fold Back

Decision Tree 8
Path Probability

\[ EV_{\text{no prophylaxis}} = (8.6 \times 0.003) + (100 \times 0.997) \]
\[ = 99.73 \]

\[ EV_{\text{prophylaxis}} = (0.2 \times 0.000012) + (99.0 \times 0.499988) + 
(8.1 \times 0.000012) + (99.7 \times 0.499988) \]
\[ = 99.35 \]

What does this mean?

- The expected value of choosing no prophylaxis is 99.73.
- The expected value of choosing prophylaxis is 99.35.
Steps in Decision Analysis

1. Imagine the model, and draw the tree
2. Identify the probabilities
3. Identify the outcome values
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Decision Tree 9

Sensitivity Analysis on Probability of HIV Without Prophylaxis

Probability of HIV without prophylaxis = 0.007
EV = 99.34 utiles
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* As opposed to superficial injury (scratch, no blood) or moderate injury (skin penetrated and blood appeared)

Sensitivity Analysis on Probability of HIV and Reduction in pHIV by drugs

- No prophylaxis
- Prophylaxis

CDC Recommendations

Blood or visibly bloody fluids or other potentially infectious material (e.g., semen; vaginal secretions; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) are the only source fluids that carry meaningful risk. Exposure to saliva, tears, sweat, or non-blood urine or feces does not require PEP.
**CDC Recommendations**

**Two Drugs**
- Zidovudine, 600 mg daily, given BID or TID
- Lamivudine, 150 mg twice daily
- Other options

**Three Drugs**
- Add Indinavir, 800 mg Q 8h on an empty stomach, and drink 1.5 L of water daily
- Other options

**Percutaneous Injuries**

**Less Severe Injury**
- Donor HIV neg Not warranted
- Donor HIV unk Generally not warranted
  - Class 1 donor Recommend 2 drugs
  - Class 2 donor Recommend 3 drugs

**More Severe Injury**
- Class 1 donor Recommend 3 drugs
- Otherwise, same recommendations

**Outcome is Cost**

Choose

- No prophylaxis
  - HIV
    - No HIV
      - Cost: $0
  - No HIV
    - Cost: $1,000

- Prophylaxis
  - HIV
    - No HIV
      - Cost: $100,000
    - Side effects
      - Cost: $101,100
  - No side effects
    - Cost: $101,000

Outcome is Cost

Incremental Cost-Effectiveness Ratio

(Cost of A) - (Cost of B)

(Effectiveness of A) - (Effectiveness of B)

No Prophylaxis "Dominates" Prophylaxis

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<th>Choice</th>
<th>Cost</th>
<th>Effectiveness</th>
</tr>
</thead>
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<tr>
<td>No Prophylaxis</td>
<td>$300.00</td>
<td>99.73 utiles</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>$1052.40</td>
<td>99.35 utiles</td>
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Disadvantages of Decision Analysis

• Time consuming
• Results difficult to explain
• Methods not well understood or trusted by policy makers

Advantages of Decision Analysis

• Forces a systematic examination of the problem
• Forces the assignment of explicit values
• Controls complexity and thus avoids processing errors

How to Use Decision Analysis

• To organize the issues for traditional decision making
• To identify a critical element for intensive study
• To provide information (not answers) for decision making
Reference