Decision Analysis Example

Prophylaxis after Occupational Exposure to HIV

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

- 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

- 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 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).
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

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

*Only recently recommended for prophylaxis
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 nonHCWs (large inoculum)
  – 1 blood transfusion
  – 1 suicidal self-innoculation
  – 1 assault on a prison guard with a needle-syringe
  – 2 intravenous exposures during procedures

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**CDC Case-Control Study of HCWs**

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<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 3-4 weeks

HIV Infection reduced by 79% (95% CI 43-94%)

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**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 effect</td>
<td>75</td>
<td>26</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

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**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

Choose → Prophylaxis

Decision Tree 2

Choose → No prophylaxis

Choose → HIV

Choose → No HIV

Choose → Prophylaxis
Rule 1

Node branches must be exhaustive and mutually exclusive.

Rule 2

At each chance node, the sum of the branch probabilities must equal one.

Decision Tree 3

Choose

- No prophylaxis
  - HIV
    - No HIV
  - Side effects
    - No side effects
- Prophylaxis
Steps in Decision Analysis

1. Imagine the model, and draw the tree
2. Identify the probabilities
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5. Perform sensitivity analyses
Proportion of health care workers infected after percutaneous exposure

<table>
<thead>
<tr>
<th>Zidovudine alone</th>
<th>Lamivudine + Indinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0006 (0.003 x 0.2)</td>
<td>?</td>
</tr>
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</table>

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

- 0.02
- 0.49

1 Delta Coordinating Committee and Delta Virology Committee. AIDS. 1999;13:57-65.

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

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

1. Imagine the model, and draw the tree
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Two Methods

• Average out and fold back
• Path probability

Decision Tree 6
Decision Tree 7

Average Out and Fold Back

Average Out

(Probability * Outcome Value)

+ (Probability * Outcome Value)

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
4. Calculate expected values
5. Perform sensitivity analyses

Decision Tree 9

Choose

No prophylaxis

HIV

pHIV=0.003
Reduce=0.008

No HIV

8.6

100

Prophylaxis

Side effects

HIV

pHIV Reduce

No HIV

0.2

99.0

No side effects

HIV

pHIV Reduce

No HIV

8.1

99.7

Sensitivity Analysis on Probability of HIV Without Prophylaxis

Probability of HIV without prophylaxis = 0.007
EV = 99.34 utiles
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).

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

Old CDC Recommendations

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

**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

Current CDC Recommendations (Beginning September 2013)

Post-exposure prophylaxis medication regimens should contain 3 (or more) antiretroviral drugs for all occupational exposures to HIV.

Reference

Incremental Cost-Effectiveness Ratio

$$\frac{(\text{Cost of A}) - (\text{Cost of B})}{(\text{Effectiveness of A}) - (\text{Effectiveness of B})}$$
### No Prophylaxis “Dominates” Prophylaxis

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<tr>
<th>Choice</th>
<th>Cost</th>
<th>Effectiveness</th>
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<tr>
<td>No Prophylaxis</td>
<td>$979.50</td>
<td>99.73 utiles</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>$1057.84</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

Amniocentesis and sampling of chorionic villi can diagnose trisomy 21 accurately, but they can lead to miscarriages (1-2 per 100 tests). Screening tests such as ultrasound (to estimate translucency under the skin behind the baby’s neck) and markers in maternal serum (hCG, free beta hCG, AFP, and estriol) can estimate the risk of trisomy 21 but not confirm it or rule it out with confidence. When these screening tests first became available, if the mother was ≥35 years of age, amniocentesis and chorionic villus sampling were offered without prior screening using ultrasound or serum markers. If she were <35 years of age, screening was done first to estimate the level of risk, and amniocentesis and chorionic villus sampling were offered only to high-risk women. Today, most women are screened regardless of age, and amniocentesis and chorionic villus sampling are offered only to high-risk women.
Cell-free fetal DNA (cffDNA) originates from trophoblasts in the placenta, circulates in maternal blood, and constitutes 2-6% of the DNA in maternal blood. cffDNA can be detected as early as 7 weeks after gestation starts. The amount increases as pregnancy progresses, and it is no longer detectable 2 hours after birth. cffDNA testing has no risk of miscarriage because it requires only a blood sample from the mother.

“Recent advances in cell-free fetal DNA (cffDNA) technology have resulted in very high detection rates for trisomy 21 (c. 99%) with false-positive rates below 1%7–10. . . . the American College of Obstetricians and Gynecologists (ACOG) has recommended a hybrid approach to cffDNA screening whereby patients ≥35 years of age are considered at sufficiently high risk to be eligible for . . . cffDNA screening while patients <35 years of age are to be screened first with one of the traditional screening protocols11.”

“. . . [Also.] primary screening [of all pregnant women] with cffDNA has been suggested12 . . . . [In addition,] recent studies indicate that a contingent approach to cffDNA screening, in which a high-risk group is identified initially through traditional and less expensive screening methods and only patients in this group are offered cffDNA screening, may be more cost-effective13–15.”
Problem
Create a decision tree for examining the consequences of different programs that use the cell-free fetal DNA test to screen pregnant women for fetuses that have trisomy 21.

Choose

Screen everyone with cfDNA.
Start with traditional screening, then add cfDNA when pregnancy is hi risk.
If ≥ or = age 35, use cfDNA; if < 35, start with traditional screening, then add cfDNA when pregnancy is hi risk.
Pseudohomework 1

For the purposes of this exercise, assume that ten per cent of patients with Non Hodgkins lymphona have a newly discovered variant of the disease that is associated with a life expectancy of five years. Patients with the standard form of Non Hodgkins lymphona have a life expectancy of seven years. A new drug prolongs life for patients with the variant form of disease from five to six years, but it has no effect on patients with the standard form of disease. The drug costs $10,000 for a course of treatment. It has negligible side effects. A diagnostic test distinguishes patients with the variant form from those with the standard form of the disease. The test costs $200. It has a sensitivity of 0.70 and a specificity of 0.80 for detecting the variant form of the disease. Costs are discounted, and years of life are discounted and quality adjusted.

You are the medical director of a large HMO, and the CEO has asked you to develop a policy for using the new drug for treating patients with Non Hodgkins lymphona. A lawyer representing the families of patients with Non Hodgkins lymphona in your HMO argues that all Non Hodgkins lymphona patients should be given drug treatment because the diagnostic test misses too many people with the variant form of the disease. Your consulting group of clinical experts recommends that treatment be given only to patients with a positive test result. They note that the treatment is expensive and most patients will not benefit if it is given to every patient. The marketing director of your HMO tells you that no one should get the drug. He points out that many positive test results will be falsely positive, that patients with a false-positive test result will not benefit from the drug, and that the cost of providing the drug to patients with a positive test result will force the company either to withhold other treatments from other patients or to raise premiums, which would reduce the company's market share.

Question 1. Draw a decision tree that describes the problem. Include all the information that an analyst would need to investigate the problem.

Question 2. Calculate the expected cost of each choice in the decision tree.

Question 3. Calculate the expected number of years of life associated with each choice in the decision tree.

Question 4. Calculate the policy-relevant cost-effectiveness ratios of the choices in the decision tree.

Question 5. Which policy would you recommend? Why?