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
  - Occurs a median of 25 days after exposure
- Seroconversion
  - Median 46 days
  - By 6 months 95% have seroconverted

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
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

<table>
<thead>
<tr>
<th>Risk Factor</th>
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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-innocation
  - 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**

31 cases and 679 controls

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</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

Prophylaxis

Decision Tree 2

Choose

No prophylaxis

No HIV

Prophylaxis

HIV
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
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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5. Perform sensitivity analyses
Zidovudine alone

Zidovudine + Lamivudine + Indinavir

<table>
<thead>
<tr>
<th></th>
<th>Zidovudine alone</th>
<th>Zidovudine + Lamivudine + Indinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of health care workers infected after percutaneous exposure</td>
<td>0.0006 (0.003 x 0.2)</td>
<td>?</td>
</tr>
<tr>
<td>Proportion of HIV-infected patients with no detectable virus at 24 weeks</td>
<td>0.02</td>
<td>0.49</td>
</tr>
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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
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>
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<td>6</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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4. **Calculate expected values**
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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

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

Expected Value

Fold Back

Decision Tree 8
Path Probability

\[ EV_{\text{route}} = \sum (\text{outcome value}) \times (\text{path probability}) \]

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

\[ = 99.73 \]

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

\[ = 99.35 \]

Path Probability

- For each outcome, multiply all the branch probabilities together and then multiply the result times the outcome value
- For each decision branch, sum the products from the calculation described above

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

Sensitivity Analysis on Probability of HIV Without Prophylaxis

Probability of HIV without prophylaxis = 0.007
EV = 99.34 utiles
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Sensitivity Analysis on Probability of HIV and Reduction in pHIV by drugs

<table>
<thead>
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<th>Probability of HIV</th>
<th>Reduction in pHIV by drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>0.003</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

0.30
0.22
0.15
0.08
0.00

CDC's Recommendations for Percutaneous Injuries until 2013

**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
**CDC’s Current Recommendations**

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

**References**

Outcome is Cost

Incremental Cost-Effectiveness Ratio

\[
\frac{(\text{Cost of A}) - (\text{Cost of B})}{(\text{Effectiveness of A}) - (\text{Effectiveness of B})}
\]

No Prophylaxis "Domimates" Prophylaxis

<table>
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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>$979.50</td>
<td>99.73 utiles</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>$1057.84</td>
<td>99.35 utiles</td>
</tr>
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</table>
Disadvantages of Decision Analysis

- Time consuming
- Results difficult to explain
- Methods not well understood or trusted by some 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
Another Example

Diagnosing and Treating Gallstones

Management of Suspected Cholecodolithiasis: A Decision Analysis for Choosing the Optimal Imaging Modality

Amaseh S. Satush[1,3], Nehat B. K. Elsobhi[1], Taha M. B. Ali[1]

Introduction
After being evaluated by abdominal ultrasound or CT scan, patients with suspected choledocholithiasis may undergo additional magnetic resonance cholangiography (MRC), endoscopic ultrasonography (EUS), and endoscopic retrograde cholangio-pancreatography (ERCP) to further confirm or refute the initial diagnostic suspicion. Whereas MRC constitutes a noninvasive diagnostic test, EUS and— to a greater extent ERCP are considered more invasive methods of imaging given that patients often undergo deep sedation or general anesthesia for the procedure. Both endoscopic procedures can lead to a variety of potential adverse events. Patients may experience discomfort or pain, adverse effects of sedation, infection, pancreatitis, perforation, and intestinal bleeding. All three imaging modalities are characterized by high levels of accuracy and effectiveness [1-4]. Most reviews recommend the usage of all three modalities, depending on the pre-test probability of choledocholithiasis [5]. The clinician is left with the dilemma of how to choose among them and in what order to schedule them when using multiple procedures in sequence. A decision analysis was performed to address these questions and study the relevance of factors that might influence such choices.
Problems with the Article

- Complications other than diagnostic delay are ignored
- The possibility of surgery is ignored
- ERCP is assumed to be a perfect gold standard
- The article’s decision tree cannot be interpreted and thus the results cannot be trusted
Still Another Example

Non Hodgkins Lymphoma

For the purposes of this exercise, assume that ten per cent of patients with Non Hodgkins lymphoma 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 lymphoma 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 lymphoma. A lawyer representing the families of patients with Non Hodgkins lymphoma in your HMO argues that all Non Hodgkins lymphoma 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.

Draw a decision tree that describes the problem. Include all the information that an analyst would need to investigate the problem.
Calculate the expected cost of each choice in the decision tree.

The expected costs for the 3 choices are: $0 for the choice "don't treat anyone," $2,700 for the choice "test, treat positives," and $10,000 for the choice "treat everyone."

Calculate the expected life expectancy of each choice in the decision tree.

The expected life expectancies for the 3 choices are: 6.800 years for the choice "don't treat anyone," 6.870 years for the choice "test, treat positives," and 6.900 years for the choice "treat everyone."

The policy-relevant cost-effectiveness ratios of the choices in the decision tree.

<table>
<thead>
<tr>
<th>Choice</th>
<th>Expected Cost in Dollars</th>
<th>Expected Survival in QALYs</th>
<th>Incremental Cost in Dollars</th>
<th>Incremental Survival in QALYs</th>
<th>Incremental Cost-effectiveness Ratio in Dollars/QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don't treat anyone</td>
<td>0</td>
<td>6.800</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Test, treat positives</td>
<td>2,700</td>
<td>6.870</td>
<td>2,700</td>
<td>0.070</td>
<td>38,571</td>
</tr>
<tr>
<td>Treat everyone</td>
<td>10,000</td>
<td>6.900</td>
<td>7,300</td>
<td>0.030</td>
<td>243,333</td>
</tr>
</tbody>
</table>

Choose Treat everyone: 6.900 yrs
Which policy would you recommend? Why?