**Decision Analysis Example**

Prophylaxis after Occupational Exposure to HIV

**Options for Doing Cost-Effectiveness Analysis**

- Clinical trial
- Mathematical modeling

**Clinical Trial**

- Conduct a clinical trial
  - Randomized controlled trial
  - Cohort study
  - Case-control study
- Measure outcomes and cost
- Calculate the Incremental Cost-Effectiveness Ratio (ICER)

**Incremental Cost-Effectiveness Ratio**

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

• RCT
• 200 patients with disease
  – 100 get Drug A
  – 100 get Drug B
• Wait 5 years
• Measure
  – The cost of medical care in each group
  – The number of years of life in each group

Outcomes

<table>
<thead>
<tr>
<th>Choice</th>
<th>Cost</th>
<th>Effectiveness</th>
</tr>
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<tbody>
<tr>
<td>Drug A</td>
<td>$1,000,000</td>
<td>500 years</td>
</tr>
<tr>
<td>Drug B</td>
<td>$900,000</td>
<td>498 years</td>
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Calculation of ICER

($1 million for the group getting Drug A) - ($900,000 for the group getting Drug B)
(500 years for the group getting Drug A) - (498 years for the group getting Drug B)

$100,000 $50,000
2 years of life 1 year of life

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

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
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 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

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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

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 innoculum)
  - 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**

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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>256 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

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**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)
**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.
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Proportion of health care workers infected after percutaneous exposure

<table>
<thead>
<tr>
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<th>Zidovudine alone</th>
<th>Lamivudine + Indinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00086 (0.003 x 0.2)</td>
<td>?</td>
<td></td>
</tr>
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</table>

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

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<th>Lamivudine + Indinavir</th>
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<tr>
<td>0.04^2</td>
<td>0.40^2</td>
<td></td>
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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

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<thead>
<tr>
<th>Outcome</th>
<th>Rank</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis, no HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis, no side effects, no HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis, side effects, no HIV</td>
<td></td>
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<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
  0.50
  No side effects
  0.50
  No prophylaxis
  0.997
  No HIV
  0.003
  HIV

• No prophylaxis
  0.997

8.6
100
0.2
99.0
8.1
99.7
```

12
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

(Probability * Outcome Value) + (Probability * Outcome Value) = Expected Value

Fold Back

Decision Tree 8

Path Probability

Choose

Path Probability

HIV

No prophylaxis

No HIV

0.003

0.997

No side effects

No prophylaxis

No HIV

0.000024

0.999976

Prophylaxis

Side effects

0.50

0.50

No prophylaxis

No HIV

0.000024

0.999976

No side effects

0.50

0.50

Prophylaxis

Choose

EV_{No prophylaxis} = (8.6 \times 0.003) + (100 \times 0.997)

= 99.73

EV_{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

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Decision Tree 9
Sensitivity Analysis on Probability of HIV Without Prophylaxis

![Graph showing sensitivity analysis]

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

![Graph showing sensitivity analysis]

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

Incremental Cost-Effectiveness Ratio

\[
\frac{(\text{Cost of A) - (Cost of B)})}{(\text{Effectiveness of A) - (Effectiveness of B})}
\]
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<tbody>
<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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### Advantages of Decision Analysis
- Forces a systematic examination of the problem
- Forces the assignment of explicit values
- Controls complexity and thus avoids processing errors

### Disadvantages of Decision Analysis
- Time consuming
- Results difficult to explain
- Methods not well understood or trusted by policy makers

### 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
Background
The importance of malaria in non endemic countries remains a major cause of travel-related morbidity and the burden of travel-related hospitalization [2]. Over the last years the number of imported malaria cases increased in Switzerland and the US [3]. The majority of the imported malaria cases are reported mainly from Sub-Saharan Africa and particularly from West Africa with a case fatality rate of 1.2% (3.4) increased (5.6).

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What Africa for the last 500 to 5000, all PVH species, imported 60% of all reported malaria cases in Switzerland. Malaria prevention measures include risk assessment, prophylaxis of the patient and the use of chemoprophylaxis. The current priority chemoprophylaxis regimen for sub-Saharan Africa are mefloquine, doxycycline and chloroquine. As in many other Western countries, the Swiss public health system does not organize chemoprophylaxis for malaria. All of the malaria medications have a similar prophylaxis effectiveness through the use of their dosage per body weight and duration of prophylaxis and also in cost [5]. The burden of the imported malaria cases in Switzerland is significant with an average of 407 increased global mobility and some travel as well as the growing number of tourists from malaria endemic countries have contributed to the importation of malaria in Europe. The tourists from malaria endemic countries constitute a special risk group with high levels of malaria importation because of their exposure to malaria infected regions when they will visit their home country. 7% of the tourists of malaria patients reported in Switzerland have a foreign nationality [9]. West Africa is among the endemic regions with the highest estimated attack rates of malaria among tourists [2]. The Swiss Federal Office of Public Health (OFSP) reported an annual average of 312 malaria cases imported from non endemic to Swiss tourists in 2014 and 2015 [3]. Treatment and prevention of melioidosis is often limited by the Swiss health system. The aim of this study is to evaluate the cost effectiveness of a potential reimbursement of the cheapest regimen for chemoprophylaxis compared with the current number of no reimbursement for the patient.

Figure 1: Decision tree model to estimate cost and effectiveness of an 886 reimbursement of the cheapest malaria chemoprophylaxis regimen for travelers from Switzerland to West Africa compared to the current number of no reimbursement. The model is the same as described in the Figure.