Decision Trees

An 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
  - Evident in a median of 25 days after exposure
- Seroconversion
  - Median 46 days
  - By 6 months present in 95% of HCWs

From: CDC. MMWR 1998;47:No. RR-7.

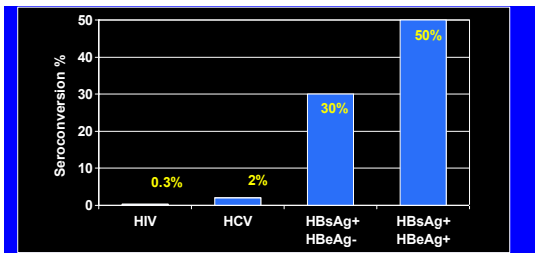
Characteristics of HIV Disease

- Mean time from infection to illness is about 10 years
- Plasma viremia is consistently present
- Drug resistance is frequent

Questions

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

Relative Risk of Seroconversion with Percutanous Injury



From: CDC. MMWR 2001;50 (RR11):1-42.

Risk of Occupational HIV Infection

As of December 31, 2013, 58 confirmed occupational transmissions of HIV and 150 possible transmissions had been reported in the United States. Of these, only one confirmed case had been reported since 1999. Underreporting of cases to CDC is possible, however, because case reporting is voluntary.

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 occupational exposure to HIV-infected blood from a needlestick or cut with a scalpel or lancet and seroconversion after the 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 and 679 Controls

Risk Factor	Adjusted Odds Ratio	95% CI
Deep Injury*	16.1	6.1 - 44.6
Visible blood from donor patient on device	5.2	1.8 - 17.7
Needle in donor patient's vein or artery	5.1	1.9 - 14.8
Terminal illness in donor	6.4	2.2 - 18.9

* 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

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-innoculation
  - 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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CDC Case-Control Study of HCWs

31 cases and 679 controls

Risk Factor	Adjusted Odds Ratio	95% CI
Zidovudine *	0.2	0.1 - 0.6

* 1000 mg/day for 3-4 weeks

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

Percentage of HCWs with Zidovudine Side Effects

Side Effect	236 using ZDV	439 without ZDV	P value
Nausea / vomiting	61	21	< 0.01
Malaise / fatigue	33	7	< 0.01
Headache	25	3	< 0.01
Myalgia/arthralgia	10	6	< 0.07
Abdominal pain	8	1	< 0.01
Diarrhea	8	2	< 0.01
Any side effect	75	26	< 0.01

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 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.
- A randomized clinical trial is not possible.
- How do we balance the benefits and risks and decide when prophylaxis should be used?

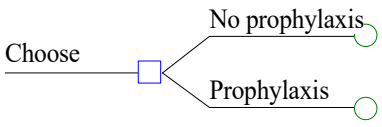
Steps in Decision Analysis

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

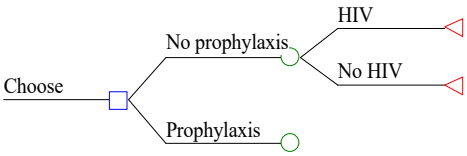
Types of Nodes

- Decision nodes (squares)
- Chance nodes (circles)
- Terminal nodes (triangles)

Decision Tree 1



Decision Tree 2



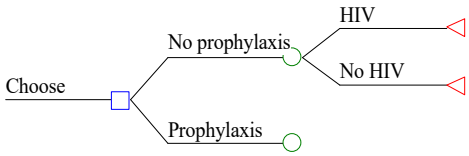
Rule 1

Node branches must be exhaustive and mutually exclusive.

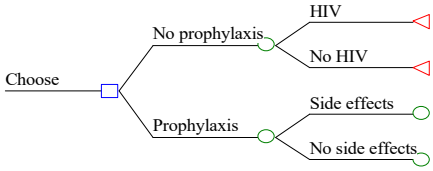
Rule 2

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

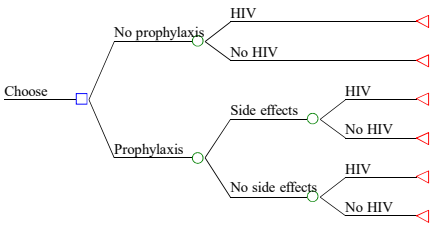
Decision Tree 2



Decision Tree 3



Decision Tree 4



Steps in Decision Analysis

1. Imagine the model, and draw the tree
2. **Identify the probabilities**
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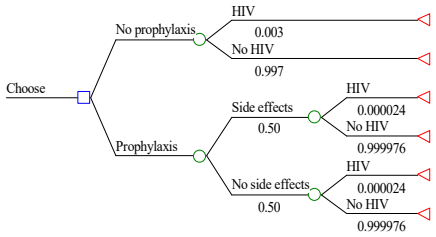
5. Perform sensitivity analyses

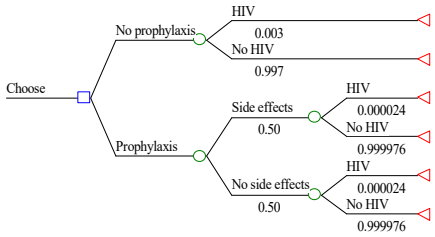
Decision Tree 5



	Zidovudine alone	Zidovudine + Lamivudine + Indinavir
Proportion of health care workers infected after percutaneous exposure	0.0006 (0.003 x 0.2)	?
Proportion of HIV-infected patients with no detectable virus at 24 weeks	0.02[1]	0.49[2]

[1] Delta Coordinating Committee and Delta Virology Committee. *AIDS*. 1999;13:57-65.
[2] Demeter LM, et al. *Ann Intern Med*. 2001;135:954-964.

Decision Tree 5



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

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

Outcome	Rank	Utility
No prophylaxis, no HIV		
Prophylaxis, no side effects, no HIV		
Prophylaxis, side effects, no HIV		
No prophylaxis, HIV		
Prophylaxis, no side effects, HIV		
Prophylaxis, side effects, HIV		

Rank and Scale Method for Measuring Utility

Outcome	Rank	Utility
No prophylaxis, no HIV	1	100.0
Prophylaxis, no side effects, no HIV	2	99.7
Prophylaxis, side effects, no HIV	3	99.0
No prophylaxis, HIV	4	8.6
Prophylaxis, no side effects, HIV	5	8.1
Prophylaxis, side effects, HIV	6	0.2

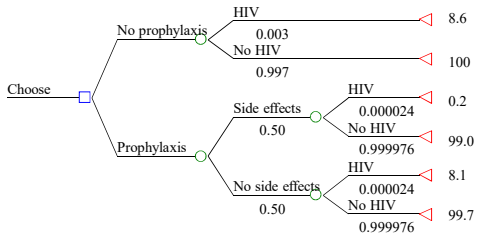
Steps in Decision Analysis

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

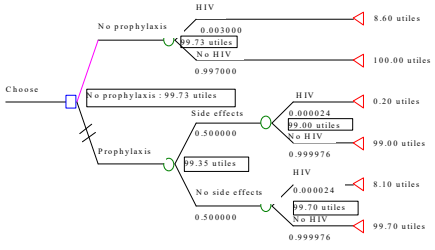
Two Methods

- Average out and fold back
- Path probability

Decision Tree 6



Decision Tree 7



Average Out and Fold Back

Average Out

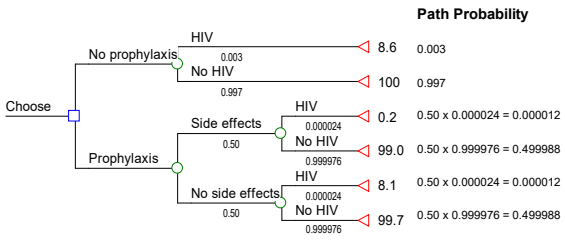
(Probability * Outcome Value)

\+ (Probability * Outcome Value)

Expected Value

Fold Back

Decision Tree 8



Path Probability

EV_{node} = Σ (outcome value) x (path probability)

$EV_{No\ prophylaxis}$ = (8.6 x 0.003) + (100 x 0.997)
= 99.73

$EV_{Prophylaxis}$ = (0.2 x 0.000012) + (99.0 x 0.499988)
+ (8.1 x 0.000012) + (99.7 x 0.499988)
= 99.35

Path Probability

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

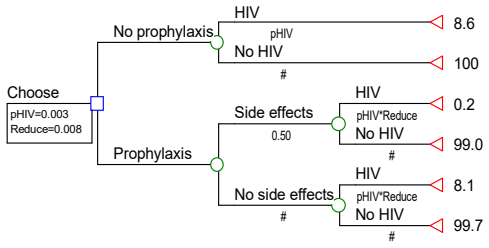
What does this mean?

- The expected value of choosing no prophylaxis is 99.73.
- The expected value of choosing prophylaxis is 99.35.

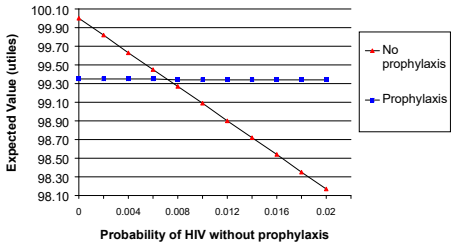
Steps in Decision Analysis

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



Threshold probability of HIV without prophylaxis = 0.007
EV = 99.34 utiles

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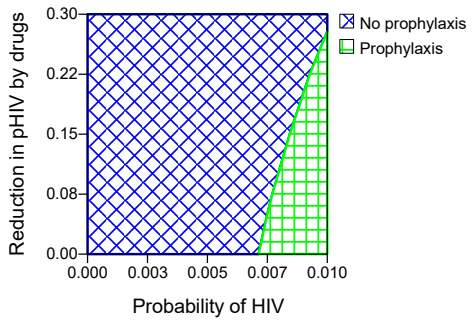


Current CDC Recommendations (Beginning September 2013)

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

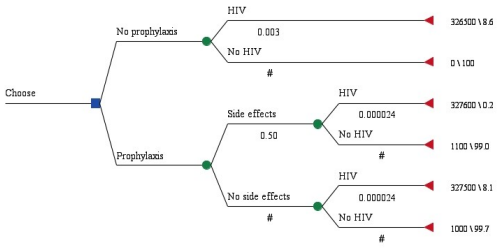
References

- Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and recommendations for Postexposure Prophylaxis. *Infection Control and Hospital Epidemiology*, Vol. 34, No. 9 (September 2013), pp. 875-892. 2015 Update: Interim Statement Regarding Potential Fetal Harm from Exposure to Dolutegravir. https://stacks.cdc.gov/view/cdc/38856/cdc_38856_DS2.pdf
- Management of sharps injuries in the healthcare setting. *BMJ* 2015;351:h3733 doi: 10.1136/bmj.h3733 (Published 29 July 2015)
- PEP [Post-Exposure Prophylaxis] Quick Guide for Occupational Exposures, Updated: July 1, 2019, http://nccc.ucsf.edu/clinical-resources/pep-resources/pep-quick-guide-for-occupational-exposures/

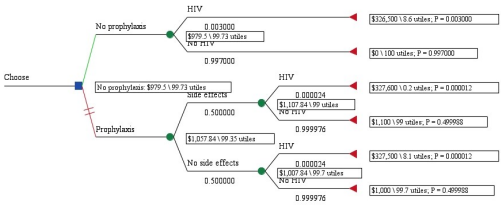
Outcome is Cost

- Lifetime cost of having HIV = $326,500
- Cost of prophylaxis = $1,000
- Cost of a side effect = $100

Outcome is Cost



Outcome is Cost



Incremental Cost-Effectiveness Ratio

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

No Prophylaxis "Dominates" Prophylaxis

Choice	Cost	Effectiveness
No Prophylaxis	$979.50	99.73 utiles
Prophylaxis	$1057.84	99.35 utiles

Disadvantages of Decision Analysis

- Time consuming
- Results difficult to explain
- Methods not well understood or trusted by many 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