



Blood-borne Pathogens and Post-Exposure Prophylaxis

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Overview

- Overview of components of a blood-borne pathogens control program
- Post-exposure Management
 - hepatitis B
 - HIV-1
 - hepatitis C

Elements of an Effective Postexposure Management Program

- Clear policies/procedures
- Training of healthcare personnel
- Rapid access to
 - clinical care
 - postexposure prophylaxis (PEP)
 - testing of source patients/HCP
- Injury prevention assessment

Exposure Control Plan

KEY ELEMENTS

- Identification of job classifications/tasks where there is exposure.
- Schedule of how/when provisions of standard will be implemented.
- Methods of communicating hazards
- Need for Hepatitis B vaccination
- Procedures for post-exposure evaluation and follow-up
- Training and its documentation
- Recordkeeping/compliance methods

Personal Protective Equipment

- Gloves
- Surgical mask
- Long-sleeved protective apparel (e.g., lab coat, gown)
- Protective eyewear with solid side shields
- Chin-length face shield worn with a surgical mask

Post-exposure Management-Overview

- Immediately report exposure incident to initiate timely follow-up process by health-care professional.
- Exposed individual must be directed to a qualified health-care professional.
- Initiate prompt request for evaluation of source individual's HBV/HCV/HIV status.

Wound Care

- Clean wounds with soap and water.
- Flush mucous membranes with water.
- No evidence of benefit for:
 - application of antiseptics or disinfectants.
 - squeezing (“milking”) puncture sites.
- Avoid use of bleach and other agents caustic to skin.

Postexposure Management: Assessment of Infection Risk

- Type of exposure
 - percutaneous
 - mucous membrane
 - non-intact skin
 - bites resulting in blood exposure
- Body substance
 - blood
 - bloody fluid
 - potentially infectious fluid or tissue
- Source person
 - presence of HBsAg
 - presence of HCV antibody
 - presence of HIV antibody
 - if source unknown, assess epidemiologic and clinical evidence

Case Presentation

- 27 yo medical exam assistant (MA) presents to Urgent Care for evaluation of needlestick injury 2 days ago from a diabetic lancet
- Source patient (SP): 35 yo male, known HIV+
- What would you do?

Case Presentation continued

- What is her risk for contracting HIV, HBV?
- Are there factors that might affect this risk?
- How effective is PEP?
- Is it too late to start PEP?
- What are the drawbacks of starting PEP?
- Which regimen(s) should be considered?
- What follow-up should be arranged?

Postexposure Management: Baseline HBV Testing of Exposed* Person

- Test for anti-HBs if person has been vaccinated, but vaccine response is unknown
- Baseline testing not necessary if exposed person has not been vaccinated or vaccine response is known

* Source HBsAg positive or status unknown

PEP for Exposure to HBV(1)

Vaccination and antibody status of exposed person

Unvaccinated:

Previously vaccinated:
Known responder

Known nonresponder

Antibody response
unknown

Treatment when source is HBsAg positive

HBIG x 1 and initiate hepatitis B vaccine series

No treatment

HBIG x 1 and initiate re-vaccination or
HBIG x 2

Test exposed person for anti-HBs
1. If adequate, no treatment
2. If inadequate, HBIG x 1
and vaccine booster

PEP for Exposure to HBV(2)

Vaccination and antibody status of exposed person

Treatment when source is not tested or status unknown

Unvaccinated:

Initiate hepatitis B vaccine series

Previously vaccinated:

Known responder

No treatment

Known nonresponder

If known high-risk source treat as if source were HBsAg positive

Antibody response unknown

Test exposed person for anti-HBs
1. If adequate, no treatment
2. If inadequate, vaccine booster and recheck titer in 1-2 mos

Efficacy of HBV PEP*

Regimen

Multiple doses of HBIG
alone when 1st dose
initiated within 1 week

Hepatitis B vaccine
series alone

Combination of HBIG
and vaccine series

Prevention of HBV

Infection

70-75%

70-75%

85-95%

* Based on perinatal data

Long-Term Efficacy

- Anti-HBs titers decline to <10 mIU/mL in 30-50% of adults within 8-10 years after vaccination
- Exposure to HBV results in anamnestic anti-HBs response that prevents clinically significant HBV infection
- Immune memory remains intact for at least 20 years after immunization
- Chronic HBV infection rarely documented among vaccine responders
- **Routine Booster doses currently not recommended**

Follow-up HBV Testing of Exposed Person

- Perform follow-up anti-HBs testing in healthcare personnel who receive hepatitis B vaccine
 - test for anti-HBs 1-2 months after last dose
 - anti-HBs response to vaccine cannot be ascertained if HBIG received in the previous 3-4 months

HBV Postexposure Counseling

- Refrain from donating blood, plasma, organs, tissue, or semen.
- No need for:
 - modification of sexual practices or refraining from becoming pregnant
 - special precautions to prevent secondary transmission.
 - modification to patient care responsibilities for exposed person
- If acute HBV infection, evaluate according to published recommendations

What is her risk of
contracting HIV?

What factors affect this risk?

Risk of HIV Transmission Following Percutaneous (Needlestick) Exposure

- Pooled analysis of prospective studies on health care workers with occupational exposures suggests risk is approximately 0.3% (95% CI, 0.2% - 0.5%)
- Mucous Membrane 0.09%
- Non-intact skin <0.1%
- Presence or absence of key risk factors may influence this risk in individual exposures

Bell DM. Am J Med 1997;102(suppl 5B):9-15.

Exposure Risks (average, per episode, involving HIV-infected source patient)

Percutaneous (blood) ¹	0.3%
Mucocutaneous (blood) ²	0.09%
Receptive anal intercourse ³	0.3 - 3%
Insertive anal intercourse ⁴	0.06%
Receptive vaginal intercourse ⁵	0.1 – 0.2%
Insertive vaginal intercourse ⁶	0.03 – 0.14%
Receptive oral (male) ⁷	0.06%
Female-female orogenital ⁸	4 case reports
IDU needle sharing ⁹	0.67%
Vertical (no prophylaxis) ¹⁰	24%

Risk Factors for Seroconversion Following Needlesticks

- CDC-sponsored case-control study
- 33 cases, 665 controls with needlesticks from confirmed HIV+ SPs
- Zidovudine (AZT) monotherapy as PEP

Risk Factors for Seroconversion

Risk Factor	Odds Ratio*	95% CI
Deep injury	15	6.0 – 41
Visibly bloody device	6.2	2.2 – 21
Device in artery/vein	4.3	1.7 – 12
Terminally ill SP	5.6	2.0 – 16
AZT PEP	0.19	0.06 – 0.52

*p<0.01 for all

Cardo DM et al. NEJM 1997;337:1485-90

Other Likely Risk Factors

- Viral load
- Glove use
 - 50% decrease in volume of blood transmitted¹
- Hollow bore vs solid bore
 - Large diameter needles weakly associated with increased risk ($p = 0.08$)²
- Drying conditions
 - tenfold drop in infectivity every 9 hours³

1. Mast ST et al. JID 1993;168(6):1589-92.

2. Cardo DM et al. NEJM 1997;337:1485-90

3. Resnick L et al, JAMA 1986;255(14):1887-91.

How effective is PEP?

Evidence of Efficacy of PEP

- Animal models: high level of protection when started within 24 hours¹
- OR = 0.19 for zidovudine use in case-control study²
- Two drugs, three drugs:
 - No direct evidence that more effective than 1 drug
 - Cases of seroconversion despite 3-drug PEP imply efficacy less than 100%^{3,4}

1. Tsai C-C et al. J Virol 1998;72:4265-73.

2. Cardo DM et al. NEJM 1997;337:1485-90.

3. Jochimsen EM et al. Arch Int Med 1999;159:2361-3.

4. MMWR June 29, 2001 / 50(RR11);1-42

Human Studies of HIV PEP Efficacy

- Little information on efficacy of PEP in humans
- Seroconversion infrequent following occupational exposure to HIV-infected blood
- Use of zidovudine (ZDV) was associated with an 81% decrease in the risk for HIV infection
 - limitations include a small number of cases, and that cases and controls came from different cohorts (*Cardo et al, NEJM 1997;337:1485-90.*)

Human Studies: Prevention of Perinatal Transmission

- ZDV administered during pregnancy, labor, and delivery reduced transmission by 67%
(Connor EM, et al. N Engl J Med 1994;331:1173-80.)
- Protective effect only partially explained by reduction in maternal viral load
- Protective effect observed when ZDV given only to newborn within the first 48-72 hours of life
(Wade NA, et al. N Engl J Med 1998;339:1409-14.) (Musoke P, et al. AIDS 1999;13:479-86.) (Guay LA, et al. Lancet 1999;354:795-802.)

Animal Studies of PEP Efficacy

- Data have been difficult to interpret and extrapolate to humans, but provide encouraging evidence of PEP efficacy
- Different virus strains, route of inoculation, dose of inocula, and drug regimens used
- Delaying time to PEP, shortening the duration, or decreasing the dose reduced effectiveness of PEP

Animal Model Evidence for Efficacy

- Macaque model: IV inoculation with SIV.
- PMPA prophylaxis started 48 h before, 4 h after or 24 h after inoculation and continued for 28 days. Controls untreated.
- No treated animal were infected; all controls were infected.

Tsai CC et al. Science 270:1197-1199.

When should PEP be started?

Timing of PEP: what's the evidence?

- Animal models and animal PEP studies: suggest substantially less effective beyond 24 - 36 hours^{1,2}
- Case-control study: most subjects in each group received PEP within 4 hours³
- Analysis of PEP failures does not suggest a clear cut-off⁴

1. Tsai C-C et al. J Virol 1998;72:4265-73.
2. Shih CC et al. JID 1991.
3. Cardo DM et al. NEJM 1997;337:1485-90.
4. MMWR June 29, 2001;50(RR11);1-42.

Timing

- Macaques inoculated IV with SIV
- PEP with PMPA for 28 d initiated 24, 48 and 72h after inoculation. Controls mock treated.
 - All controls infected
 - All animals treated at 24 h protected
 - Half of the animals in the other treatment groups showed persistent viremia.

Tsai CC et al. J Virology 1998

Timing of PEP: An Anecdote

- 13 yo girl in Italy transfused with one unit of blood from donor who was acutely infected with HIV but not yet HIV-antibody positive
- Seroconversion risk estimated to be virtually 100%
- 3-drug PEP initiated 50 hours post-transfusion, continued for 9 months
- No evidence of HIV infection 15 months later

How long (duration)?

- Macaques inoculated IV with SIV
- PEP with PMPA initiated at 24 h after exposure, and continued for 3, 10 and 28d.
 - All animals treated for 28 days protected.
 - $\frac{1}{4}$ animals treated for 10 days had persistent infection, $\frac{3}{4}$ with antibody response,
 - $\frac{2}{4}$ animals treated for 3 days had persistent infection, $\frac{4}{4}$ with antibody response.

Duration of PEP

- In animal model, 28 days more effective than 10 days or 3 days of PEP¹
- 4 weeks (28 days) used in case-control study² and recommended by CDC guidelines³

1. Tsai C-C et al. J Virol 1998;72:4265-73.

2. Cardo DM et al. NEJM 1997;337:1485-90.

3. MMWR June 29, 2001;50(RR11);1-42.

Failures in Healthcare Personnel*

World-wide Cases

- 16 cases of ZDV failure in healthcare personnel
- 5 cases of combination HIV PEP failure
- no delay in time to seroconversion
- no adverse effects on natural history

Potential Explanations

- delay in treatment
- dose too low / low drug levels
- resistant virus
- high inoculum exposure
- treatment duration too short

*Beltrami EM. *Semin Infect Control* 2001;1:2-18

Reported Failures of Combination HIV PEP*

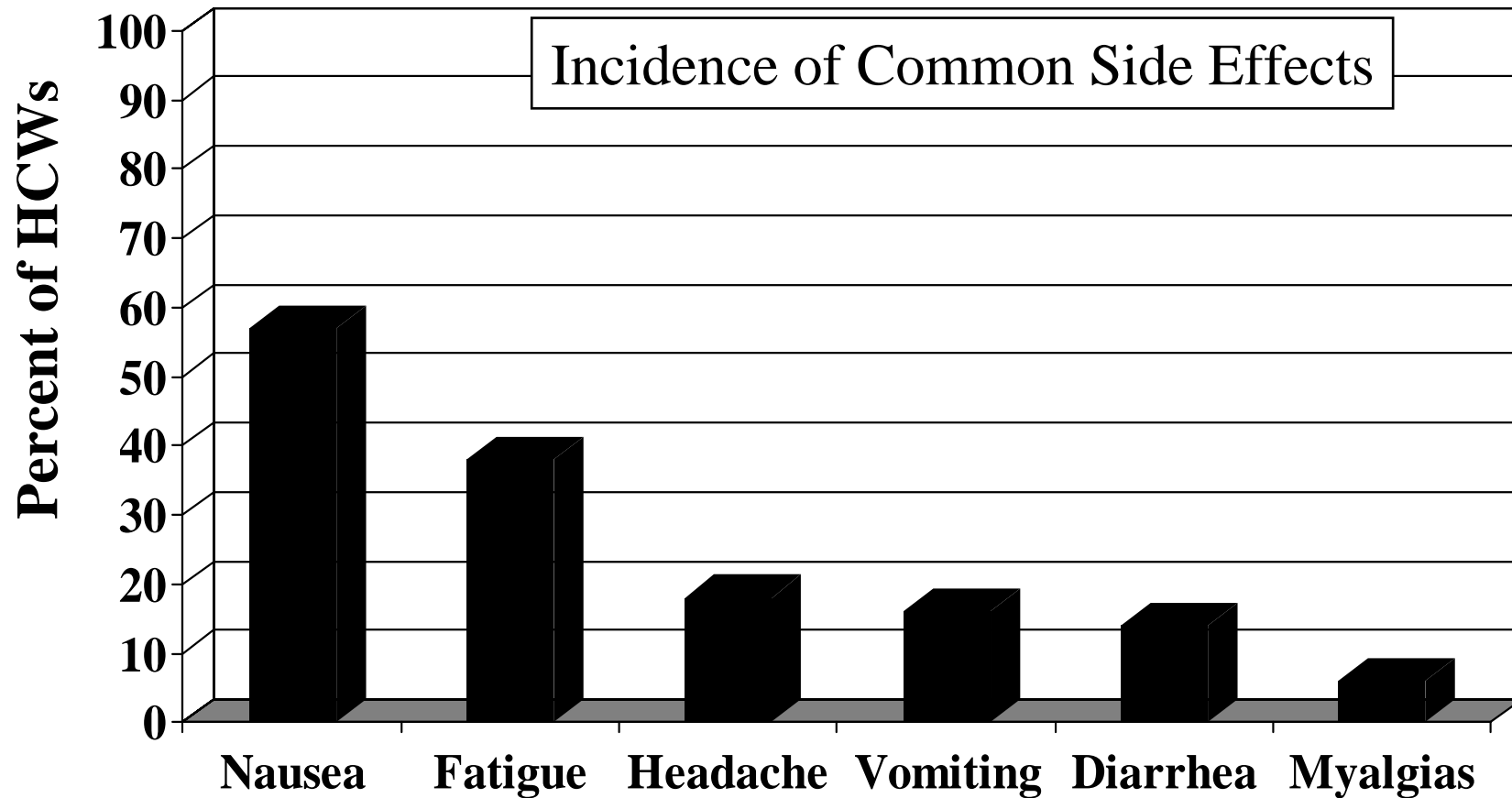
<u>Injury</u>	<u>Regimen</u>	<u>Source on</u>
	Antiretroviral?	
Biopsy needle	ZDV, ddl	yes
Hollow needle	ZDV, ddl	no
Large-bore hollow needle resistant)	3 drugs	yes (not
Hollow needle	ZDV, 3TC, ddl, IDV	yes (resistant)
Unknown sharp	ddl, d4T, NVP	yes (resistant)

All HCP seroconverted within 100 days of exposure

*Beltrami EM. *Semin Infect Control* 2001;1:2-18

What are the drawbacks of
PEP?

Tolerability of HIV PEP in Health Care Workers



Nausea Fatigue Headache Vomiting Diarrhea Myalgias
Wang SA. Infect Control Hosp Epidemiol 2000;231:780-5.

Back to the Case

- 27 yo Medical Assistant presents to Urgent Care for evaluation of needlestick 2 days ago from a diabetic lancet
- Source patient (SP): 35 yo male, known HIV+
- What other questions do you have for her?

Back to the Case

- According to the MA, the SP has never received treatment for his HIV. She does not know his VL or CD4 count, but “he looks pretty healthy.”
- The lancet was visibly bloody and stuck her through her glove, causing her to bleed
- Exam: pinpoint puncture wound on thumb
- What are your PEP recommendations?

Evaluating the Source for HIV

- EIA
 - Consider rapid test if EIA testing cannot be completed within 24-48 hours
- Confirmation of reactive result not necessary for PEP management
- Direct virus assays (e.g., PCR, p24 antigen) not recommended

Which PEP regimen should be considered?

Recommendations-Percutaneous Injuries

Infection Status of Source

Exposure Type	HIV positive, class 1	HIV positive, class 2	HIV status unknown
Less Severe	Recommend basic PEP	Recommend expanded PEP	Generally, no PEP
More Severe	Recommend expanded PEP	Recommend expanded PEP	Generally, no PEP

Class 1: Asymptomatic or known low viral load

Class 2: Symptomatic, AIDS, or known high viral load

Recommendations Mucous Membrane and Non-Intact Skin Exposures

Infection Status of Source

Exposure Type	HIV positive, class 1	HIV positive, class 2	HIV status unknown
Small Volume (e.g., few drops)	Consider basic PEP	Recommend basic PEP	Generally, no PEP
Large Volume (e.g., major blood splash)	Recommend basic PEP	Recommend expanded PEP	Generally, no PEP

Class 1: Asymptomatic or known low viral load
 Class 2: Symptomatic, AIDS, or known high viral load

PEP Regimens: Basic regimens

- Two NRTIs
- Simple dosing, fewer side effects
- Preferred basic regimens:
 zidovudine (AZT) OR tenofovir (TDF)
 plus
 lamivudine (3TC) OR emtricitabine (FTC)
- Alternative basic regimens:
 stavudine (d4T) OR didanosine (ddI)
 plus
 lamivudine (3TC) OR emtricitabine (FTC)

Expanded PEP Regimens

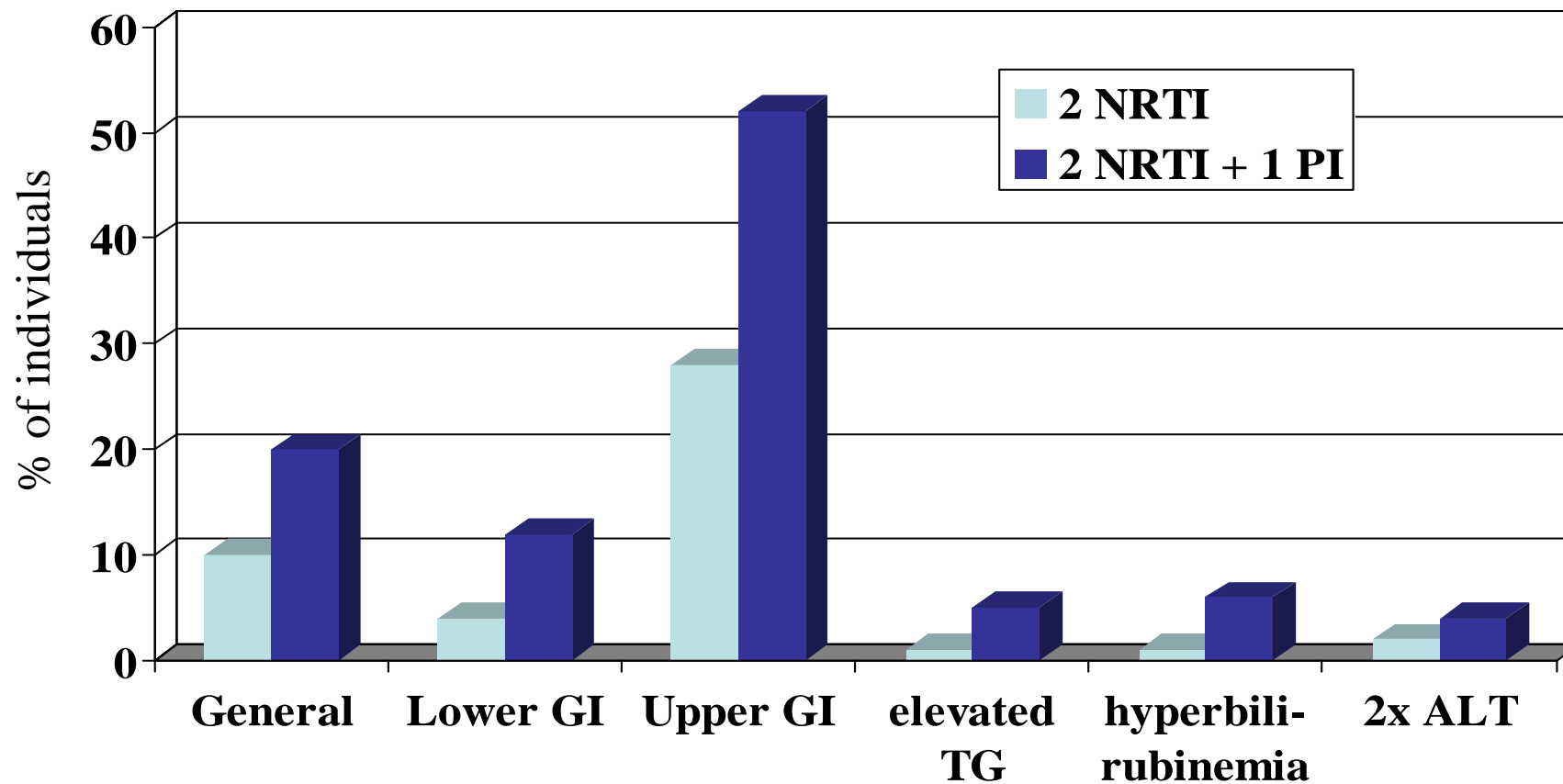
- Basic regimen plus a third agent
- Rationale: 3 drugs may be more effective than 2 drugs, though direct evidence is lacking
- Consider for more serious exposures or if resistance in the source patient is suspected
- Adherence more difficult
- More potential for toxicity

Expanded PEP Regimens

- Preferred Expanded Regimen:
 - Basic regimen plus lopinavir/ritonavir (*Kaletra*)
- Alternate Expanded Regimens:
 - Basic regimen plus one of the following:
 - Atazanavir* +/- ritonavir
 - Fosamprenavir +/- ritonavir
 - Indinavir +/- ritonavir
 - Saquinavir (hgc; *Invirase*) + ritonavir
 - Nelfinavir
 - Efavirenz

*Atazanavir requires ritonavir boosting if used with tenofovir

Adverse Effects: Basic vs Expanded Regimens



Back to the Case

- After extensive counseling, she decides to take zidovudine + lamivudine (*Combivir*) basic regimen
- You write the prescription and arrange for follow-up, but before the patient leaves, the triage nurse informs you that she has finally tracked down the SP's Primary Care Provider

Back to the Case, continued

- The SP's PCP tells you the following:
 - His CD4 count was 450 cells/mm³ two months ago, his CD4 nadir is 280 cells/mm³, he has never had an OI.
 - SP is not naïve to therapy; for the past year he has been on AZT/3TC/RTV/IDV (1st regimen).
 - Viral load 2 months ago was around 60,000 copies/mL.
- What do you do with this information?

Case: PEP options

- Source patient's high-level VL despite ART suggests that he is either not taking his medications, or that he has developed resistance to his regimen
- Turn-around time for a resistance assay too long for this to be a useful tool in designing her PEP regimen
 - Must make best guess about patterns of anticipated resistance to SP's regimen
- If resistance has developed, would suspect resistance to lamivudine, zidovudine, and possibly ritonavir/indinavir
- Cross-resistance considerations would suggest that resistance to stavudine and abacavir may also exist; resistance to tenofovir and didanosine also possible but less likely

Case: PEP options

- Given concerns over efficacy of a 2-NRTI regimen, would recommend a 3 or 4 drug PEP regimen
- Resistance to PIs: difficult to estimate, but PI resistance generally evolves less rapidly than does resistance to the NRTI components of typical ART regimens
- Would not expect any resistance to NNRTI class
- One reasonable PEP regimen: tenofovir + d4T + (efavirenz OR lopinavir/ritonavir)
- Notes:
 - Efavirenz is contraindicated in pregnancy
 - Combining ddI + tenofovir + efavirenz no longer recommended in ART regimens

Monitoring for PEP Toxicity

- Tests at baseline and 2 weeks after starting PEP
 - complete blood count
 - renal and hepatic profiles
- Follow-up testing if taking protease inhibitor
 - monitor for hypoglycemia
 - monitor for crystalluria, hematuria, hemolytic anemia, and hepatitis if on indinavir
- Modify regimen if toxicity noted
- Expert consultation encouraged

Case 2: Splash!

- 24 yo dental technician splashed in the eye during dental procedure 3 hours ago
- Source patient: 33 yo male, co-infected with HIV and HCV
- What else do you want to know?

Which fluids are potentially infectious for HIV?

- blood?
- saliva?
- sweat?
- feces?
- spinal fluid?
- pleural fluid?
- pus?
- urine?

Which fluids are potentially infectious for HIV?

- blood
- saliva
- sweat
- feces
- spinal fluid
- pleural fluid
- pus
- urine

Case 2-continued

- Saliva was visibly bloody - in fact, it was mostly blood that splashed her
- She rinsed out her eye immediately
- Source patient has never taken antiretrovirals, has a CD4 count of “about 500” and a viral load of 20,000 last time it was checked
- The technician is 8 weeks pregnant

Case 2-continued

- What is her risk of contracting HIV? Of HCV?
- What are your PEP recommendations?
- How does her pregnancy affect your decision making?

Case 2 continued

- Risk of HIV from mucous membrane exposures: 0.09% (95% CI 0.006% -0.5%)¹
- Risk of HCV in this circumstance unknown; thought to be higher than HIV, because risk of HCV in percutaneous exposures of 1.8%,²⁻⁴ is higher than that for HIV

1. Ippolito G et al. Arch Int Med 1993;153:1451--8.

2. Lanphear BP et al. Infect Control Hosp Epidemiol 1994;15:745-50.

3. Puro V et al. Am J Infect Control 1995;23:273-7.

4. Mitsui T et al. Hepatology 1992;16:1109-14.

PEP in Pregnancy

- Most antiretrovirals are pregnancy class B or C
- Antiretroviral Pregnancy Registry has not detected increased teratogenic risk for ARVs in general, nor specifically for AZT and 3TC, in the first trimester¹
- Avoid efavirenz (anencephaly in monkeys), amprenavir (ossification defects in rabbits), and indinavir in late term (hyperbilirubinemia)
- Theoretically higher risk of vertical transmission with primary HIV infection

1. Garcia et al. ICAAC, December 2001, Abstract 1325.

Case 2 continued

- You jointly decide on AZT/3TC/nelfinavir
- 3 days later she calls complaining of headache, an itchy rash, and URI symptoms
- What do you do?

Case 2-continued

- Exam:
 - VS - T 99.0 R 14 P 78 BP 134/76
 - Gen - alert, tired-appearing, no acute distress
 - HEENT - nasal congestion, otherwise benign
 - Neck - 3 ant cervical lymph nodes
 - Lungs, cardiac, abdomen - benign
 - Neuro - nonfocal
 - Skin - urticarial rash on trunk and legs

Case 2 continued

- What could be responsible for her symptoms?
- How would you manage her?

Could she have Primary HIV Infection?

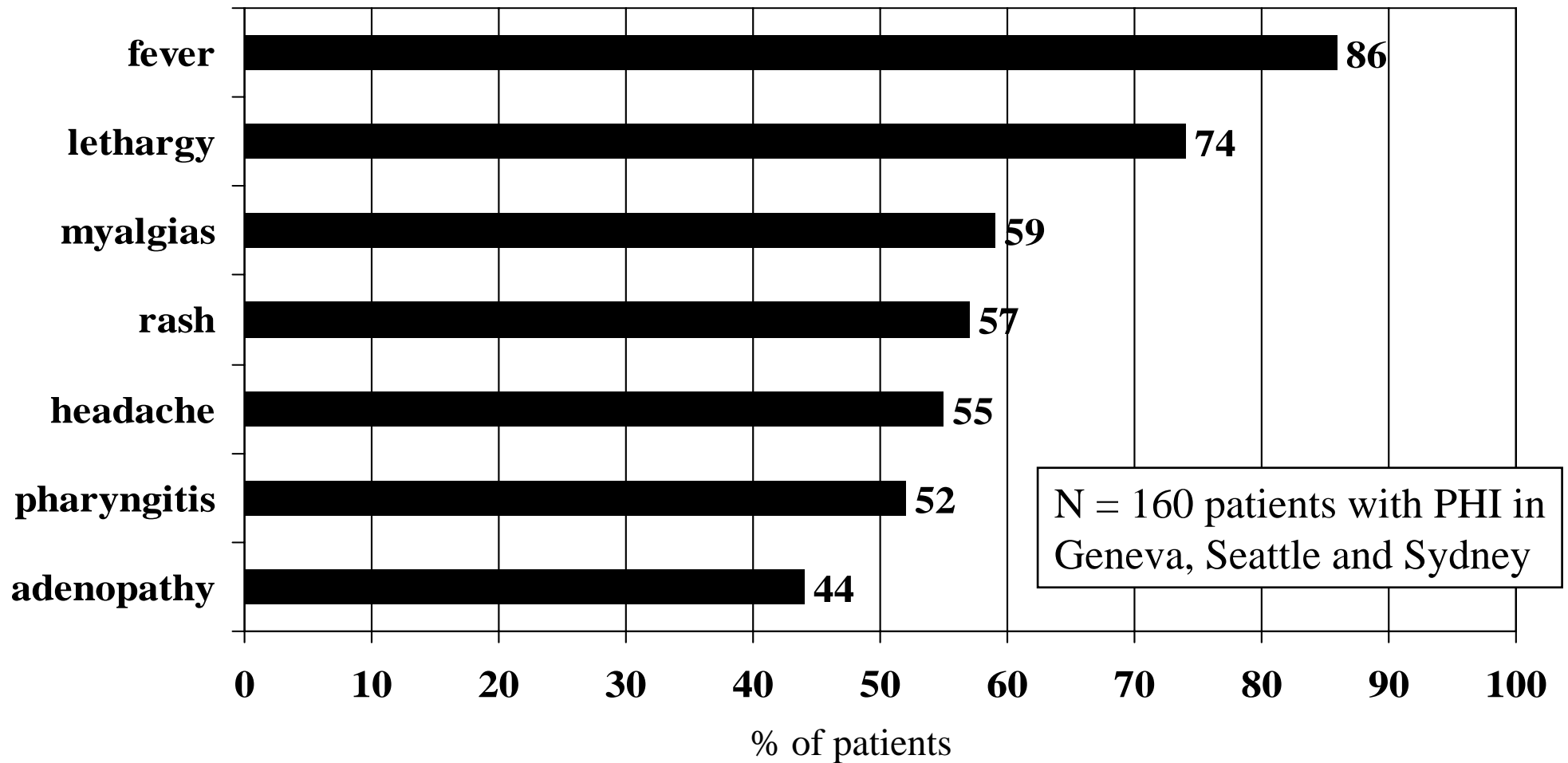
- Most patients who contract HIV are symptomatic with seroconversion¹
- Flu-like or mono-like illness often accompanied by a rash²
- Onset typically 2-6 weeks following exposure, but high variability¹
- Treatment of PHI with antiretroviral therapy may have long-term benefit³

1. Schacker T et al. Ann Int Med 1996;125:257-64.

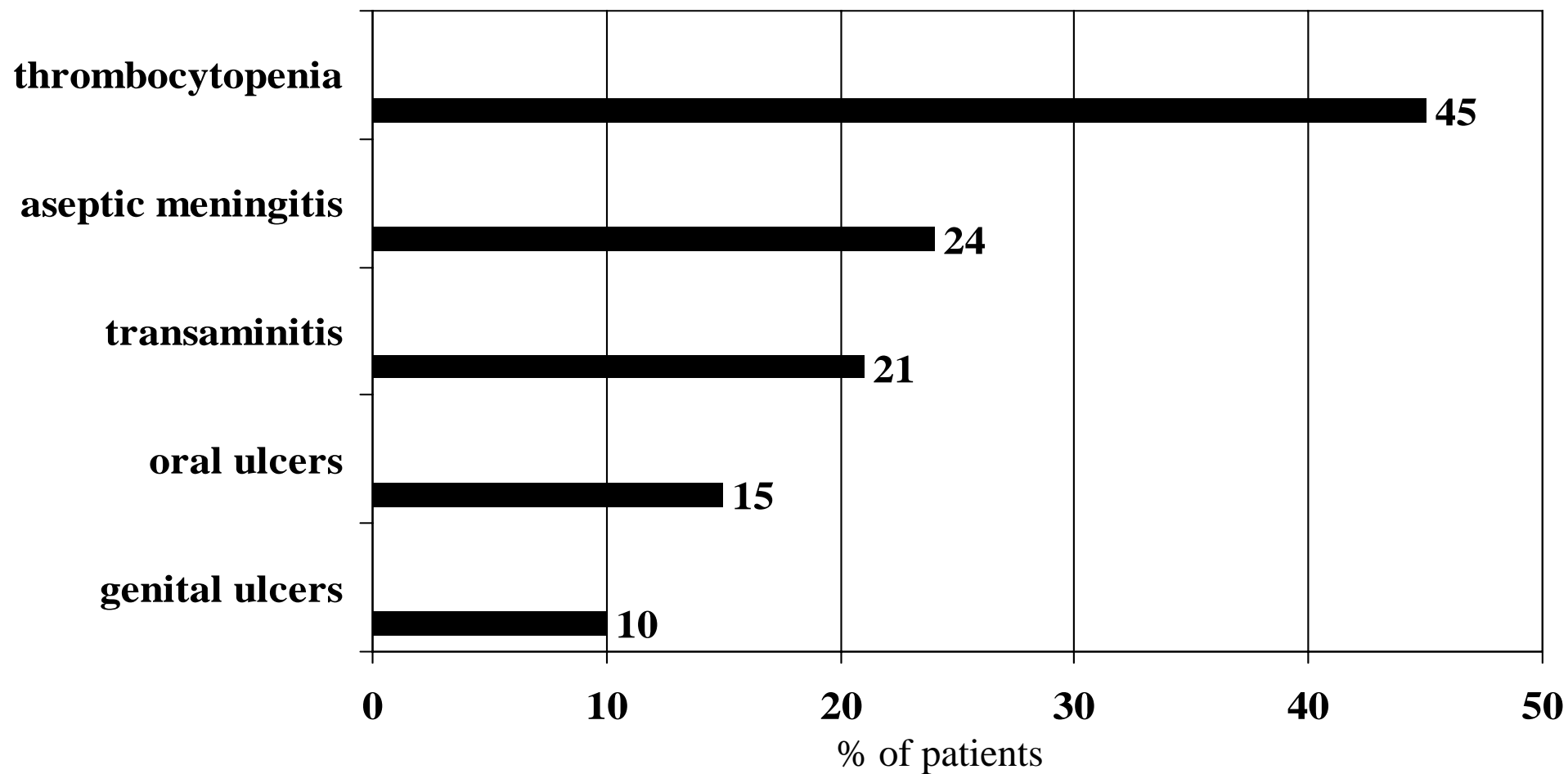
2. Kahn JO, Walker BD. N Engl J Med. 1998;339:33-39.

3. Walker B. State of the Art Lecture and Summary. 8th CROI, Session #37.

PHI: Common Signs & Symptoms



PHI: Other Signs & Symptoms



Could She Have Primary HIV Infection?

- Several features of her current illness make primary HIV infection unlikely
 - Only three days since the exposure
 - Presence of nasal congestion
 - Rash is urticarial
- However, would not be unreasonable to check an HIV viral load to rule out PHI

Follow-up HIV Testing of Exposed Person

- If source HIV positive, test at 6 weeks, 3 months, 6 months
 - EIA standard test
 - direct virus assays not recommended
- Extending follow-up to 12 months
 - recommended for HCP who become infected with HCV following exposure to co-infected source
 - optional in other situations

Hepatitis C Exposure

- Average risk of seroconversion from percutaneous exposure 1.8%¹⁻³
- Same risk factors as for HIV thought to apply
- Gamma globulin not recommended⁴
- Early recognition and treatment of *chronic* HCV infection may substantially improve odds of eradication⁵

1. Lanphear BP et al. Infect Control Hosp Epidemiol 1994;15:745-50.

2. Puro V et al. Am J Infect Control 1995;23:273-7.

3. Mitsui T et al. Hepatology 1992;16:1109-14.

4. Alter MJ. Infect Control Hosp Epidemiol 1994;15:742-4.

5. Jaeckel E et al. N Engl J Med 2001; 345:1452-1457.

Follow-up of HCV-Exposed HCP

- Test for anti-HCV and ALT 4-6 months after exposure
- Test for HCV-RNA at 4-6 weeks for earlier diagnosis of HCV infection.
- Confirm anti-HCV EIA-positive results with supplemental test (e.g., RIBA)
- No guidelines for therapy during acute infection
 - when HCV infection identified early, refer worker to a specialist for proper management
- Not recommended after exposure
 - immunoglobulin not effective
 - no data on use of antivirals (e.g., interferon), and may be effective only with established infection
 - antivirals not FDA approved for this setting

HIV Postexposure Counseling

- Side effects of PEP drugs
- Signs and symptoms of acute HIV infection
 - fever
 - rash
 - flu-like illness
- Prevention of secondary transmission
 - sexual abstinence or condom use
 - no blood/tissue donation
- Transmission and PEP drug risks if breastfeeding

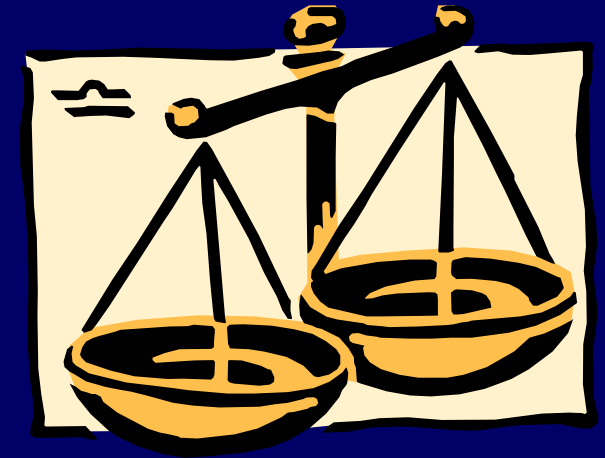
No work restriction indicated

HCV Postexposure Counseling

- Refrain from donating blood, plasma, organs, tissue, or semen.
- No need for:
 - modification of sexual practices or refraining from becoming pregnant
 - special precautions to prevent secondary transmission.
 - modification to patient care responsibilities for exposed person, even if HCV infected

Post-Exposure Prophylaxis: Core Principles

- Evidence is limited
- Balancing of risks vs benefits
- Timing: the sooner the better, but interval beyond which there is no benefit is unclear



Post-Exposure Prophylaxis: Core Principles

- Optimal duration unclear, 28 days is recommended
- Decision making can become very complex when drug resistance in the SP is suspected
- Offering non-occupational PEP is indicated for risky exposures, and does not appear to increase unsafe sexual behavior for most recipients



Sources of Additional Information

- Division of Healthcare Quality Promotion
<http://www.cdc.gov/ncidod/hip/>
- Hepatitis Hotline: <http://www.cdc.gov/hepatitis>
- Needlestick!: <http://www.needlestick.mednet.ucla.edu>
- UCSF PEP Line:
<http://www.ucsf.edu/hivcntr/Info/Contact.html>

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