Alcohol and HIV Drug Interactions

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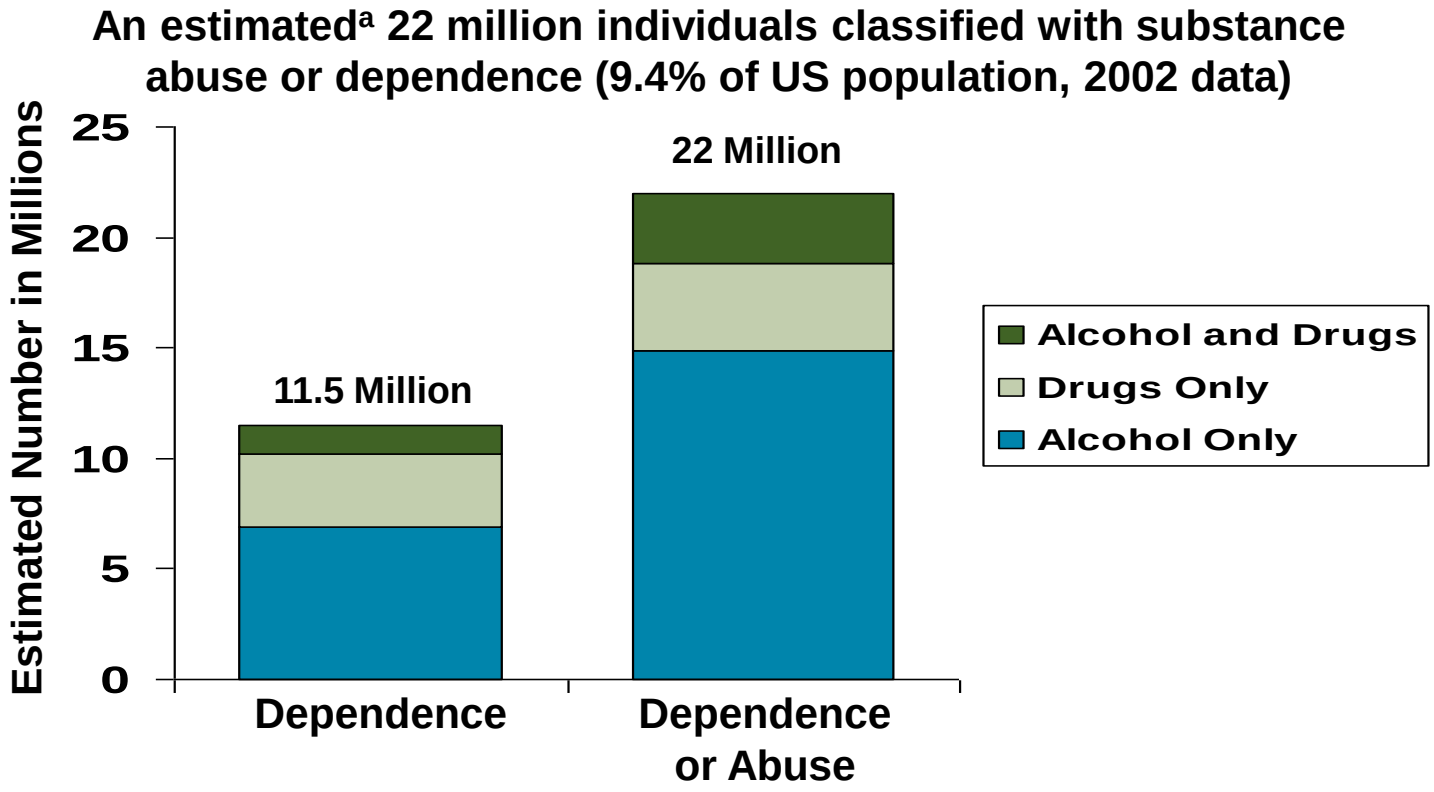
Objectives

- **Alcohol Abuse on HIV Treatment Outcomes.**
- **Relationships and interactions among alcohol, HIV drug metabolism, and pharmacogenetics.**
- **Elucidating the extent of liver toxicity due to antiretroviral therapy and drug–drug interactions.**
- **Interaction of HIV/HCV/HBV In individuals who consume alcohol.**
- **The Identification and Management of Alcohol Abuse in HIV Patients.**

The Effects of Alcohol Abuse on HIV Treatment Adherence and Outcomes

Substance Dependence and Abuse in the United States

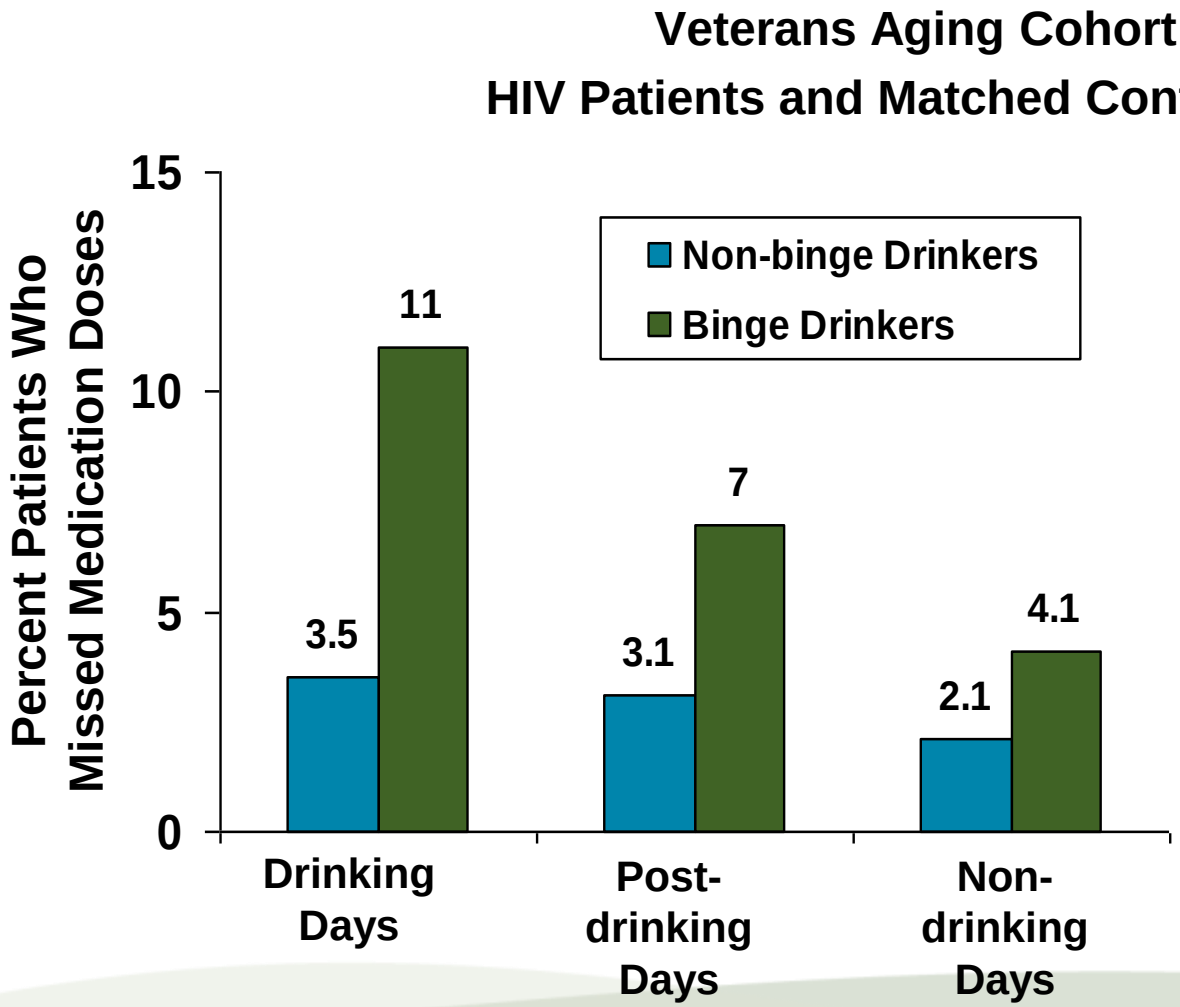


[a]**Estimated from a sample of 68,126 individuals representative of the US population.**

Substance dependence: associated with impact on health, emotional problems, attempts to cut down on use, tolerance, withdrawal, and other substance-specific symptoms.
Substance abuse: not dependent; associated with problems at work, home and school; problems with family or friends, physical danger, trouble with the law due to substance.

SAMHSA. 2002 results from the National Survey on Drug Use and Health: national findings. http://www.oas.samhsa.gov/nhsda/2k2nsduh/Results/2k2Results.htm. Accessed May 4, 2009.

Binge Drinking Is Associated With Missed Doses of ART

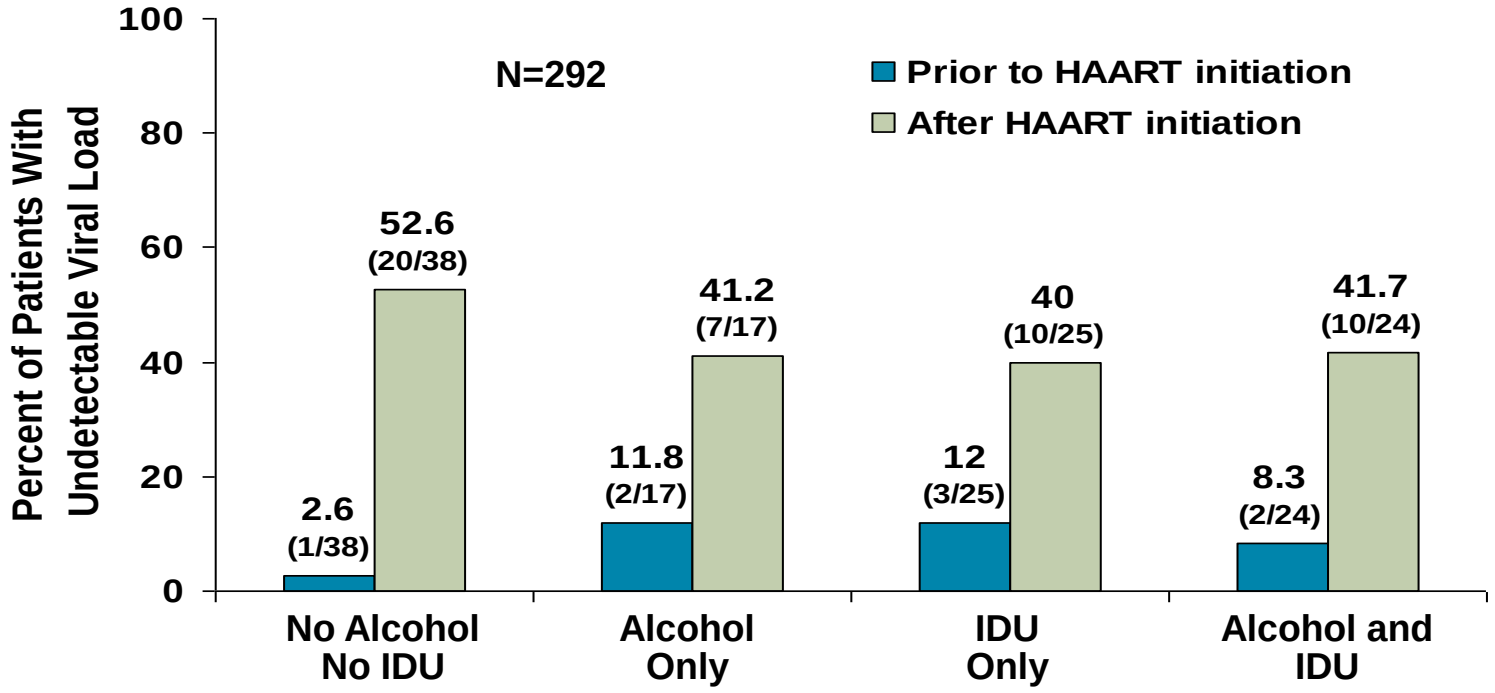


- Among patients who abstained from alcohol, 2.4% missed medication doses on a particular day
- In both non-binge and binge drinkers, alcohol consumption was associated with missed doses on that day, and for 2 days immediately subsequent

Braithwaite RS, et al. *Alcohol Clin Exp Res*. 2005;29(7):1190-1197.

Alcohol Abuse and/or IDU May Affect Response to ART

- Alcohol abuse and/or IDU were associated with reduced virologic response as compared to no alcohol/no IDU, but the difference was not statistically significant
- IDU, and alcohol abuse and IDU, were associated with significantly reduced immunologic response



Mean change CD4+ (cells/mm^3)	139	139	10 (*P*=0.037)	21 (*P*=0.038)

Henrich TJ, et al. *J Community Health.* 2008;33(2):69-77.

Alcohol Abuse May Be Associated With Delayed Presentation to HIV Care

Delay Between Positive HIV Test and Initial Presentation to Primary Medical Care (N=189)

Patient Factors	Additional Delay in Months (mean)	*P*
Not having a spouse or partner	8.6	.08
Not having a living mother	13.9	.01
Not aware of HIV risk at testing[a]	18	.001
Injection drug use	19.2	.001
Not told of HIV-positive status in person[a]	30.4	.002
Alcohol use (potential use/dependence)[b]		.03
Men	14.6	0.01
Women	-10	.16

[a] N=187

[b] Assessment based on 4-question screening tool for alcohol and/or substance abuse (CAGE); delay significant in men, not women.

Samet JH, et al. *Arch Intern Med.* 1998;158(7):734-740.

How much alcohol will affect the liver

- Research indicates that alcohol consumption greater than 50 g/day (four or five drinks) is a risk factor for liver disease progression among patients with HIV/HCV co-infection.

Pharmacogenomics and Pharmacogenetics.

- Pharmacogenomics, a function of the human genome. It uses genetic information to predict a patient's response to a drug. Examples of genes that influence a patient's response are genes that regulate the enzymes and proteins involved in drug(s) metabolism and transport, genes that code for specific drug targets, or genes that influence the expression of a disease.
- Pharmacogenetics is the field of science that identifies and characterizes polymorphic expression of genes related to drug metabolism.

PRINCIPAL CONSEQUENCES OF GENETIC POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES

- Poor drug metabolizes
- Ultra rapid Drug Metabolizes

PRINCIPAL CONSEQUENCES OF GENETIC POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES

Poor drug metabolizes:

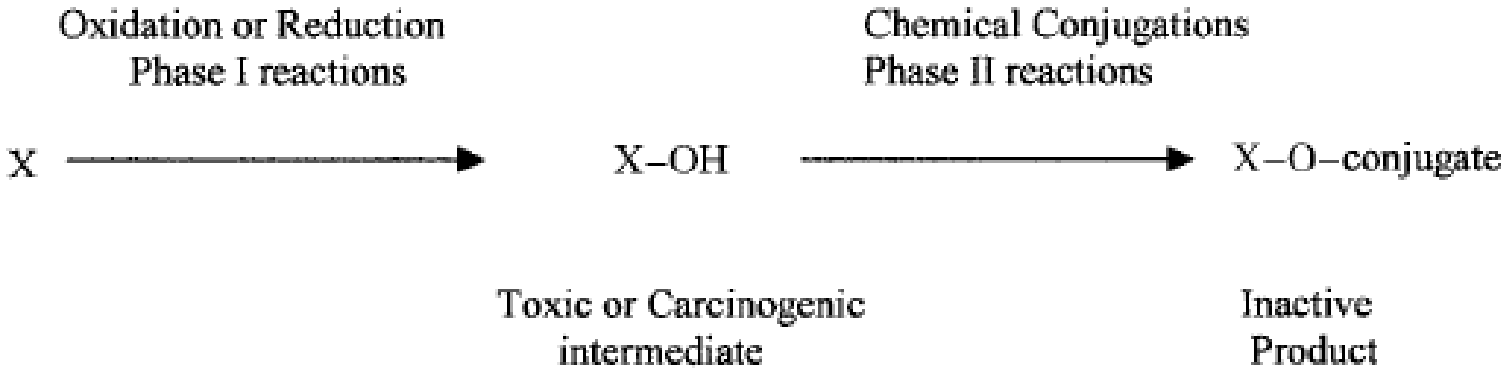
1. Homozygous for defective genes, Diminished first-pass metabolism, increased bioavailability, exaggerated response
2. Diminished drug elimination, enhanced side effects or toxic effects
3. Active metabolite not formed, loss of therapeutic efficacy.

PRINCIPAL CONSEQUENCES OF GENETIC POLYMORPHISMS OF DRUG-METABOLIZING ENZYMES

Ultra rapid Drug Metabolizes:

1. Gene duplication or amplification.
2. Lack of therapeutic effect at standard doses.
3. Too much active metabolite, adverse drug reaction.
4. Explanation for the appearance of poor medication compliance–rapid drug metabolism with no therapeutic efficacy.

Biotransformation of drugs and alcohol



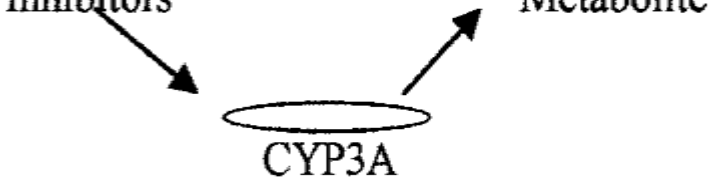
Phase I Enzymes	Phase II Enzymes
Cytochrome P450 eg. CYP3A4	Glutathione S-transferase
Alcohol dehydrogenase	N-acetyltransferases
Aldehyde dehydrogenase	Sulfotransferase
Xanthine oxidases	UDP-glucuronosyltransferases
Epoxide hydrolases	Methyltransferases

Biotransformation of drugs and alcohol

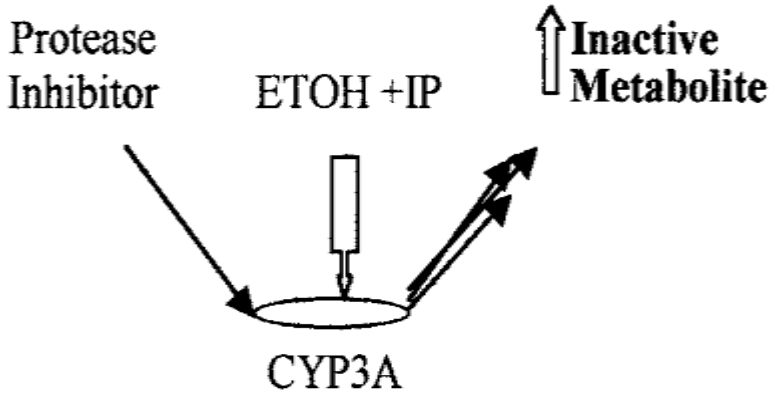
1. *Genetic polymorphisms producing rapid phase I and slow phase II reactions result in a buildup of toxic or carcinogenic reactive intermediates (X2OH) resulting in altered drug efficiency and less inactive product (X2O-conjugate).*
2. *Alternatively, in advanced liver disease phase I reactions are impaired while phase II reactions are preserved, resulting in less drug biotransformation.*

A. Inducer of CYP3A4 (alcoholic beverage- ethanol plus isopentanol , ETOH+IP)

NORMAL

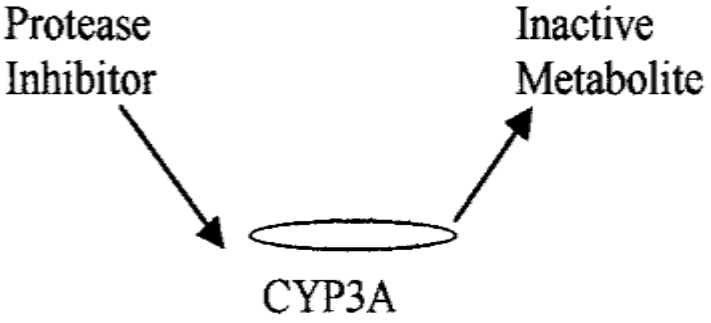


ETHANOL + ISOPENTANOL

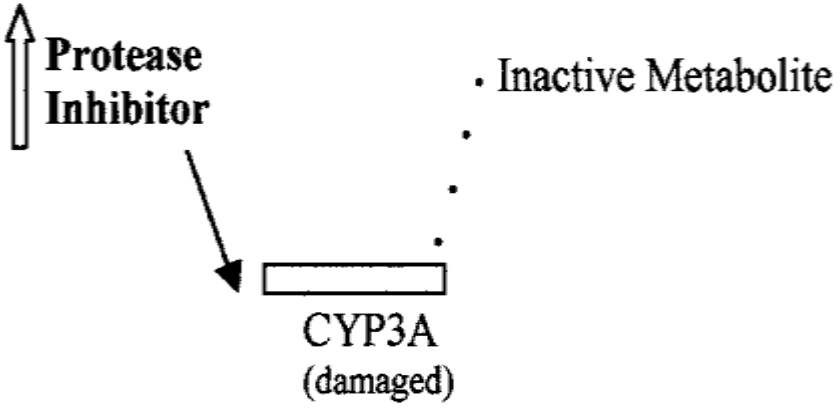


B. inhibitor of CYP3A4 (liver cirrhosis- reduced liver function)

NORMAL



LIVER CIRRHOSIS



Metabolism of Alcohol and HIV Drugs

- Most important for alcohol detoxification are alcohol dehydrogenases and glutathione-*S*-transferase. Alcohol dehydrogenase (ADH) . Among the isoforms of ADH, many result in decreased metabolism of ethanol.
- For many HIV agents, specific cytochromes of *P*-450 system and glutathione-*S*-transferases and in the intestine the P-glycoprotein are important for metabolism.
- The ethanol-inducible cytochrome P450 CYP2E1 exhibits multiple polymorphisms, however, this does not have a role in humans.

Biotransformation of drugs and Alcohol

TABLE 3. CYP2E1 POLYMORPHISMS AND POPULATIONS FREQUENCIES

Polymorphism	*Frequency (%)*	*Population*
c2/c2 (*Pst*I$^+$/*Rsa*I$^-$)	2–4	White
	20–24	Japanese
	5	African-American
CC (*Dra*I)	10	White
	25	Japanese
2E1**1D (*Xba*I)[a]	1.1–6.9	White
	31	African-American
	23	Chinese
C/D alleles	6	White
	20	Hispanics
	19	Native American
c1/c2 alleles	0	White
	15	Hispanics
	29	Native Americans

[a]*Xba*I, 100-base insertion in regulatory region of gene, modifies gene expression in the liver.

Does alcohol drinks contain only ethanol?

- In addition to ethanol, alcoholic drinks contain higher chain alcohols such as isopentanols: 3-methylbutanol and 2- methylbutanol (five carbon alcohols). The concentration of these isopentanols can range from 0.13 to 0.5% in alcoholic beverages.
- Studies with human hepatocytes have shown that isopentanol is a potent inducer of CYP3A4.
- The combination of ethanol and isopentanols synergistically act as potent inducers of P450 CYP 3A4.

Alcoholic drinks and drug interactions

- *In vivo* animal studies have shown that ethanol plus isopentanol mixtures result in enhanced hepatic levels of CYP3A activity and enhanced drug-induced liver toxicity, such as acetaminophen hepatoxicity.
- Thus individuals who consume alcoholic beverages and take HAART or other hepatotoxic drugs may be at risk for drug–drug interactions . In particular, liver damage may develop from therapeutic doses of HAART drugs or even acetaminophen.

Alcoholic drinks and drug interactions

- The metabolic picture is even more complex, because some protease inhibitors and antifungal agents used in AIDS therapy are potent *inhibitors* of CYP3A4.
- Thus, these drugs may trigger potent drug–drug interactions, sometimes for better. For example, ritonavir was found to protect hepatocytes from acetaminophen hepatotoxicity when administered simultaneously.

Alcoholic drinks and drug interactions

Thus, the risk of developing liver damage from drug–drug interactions will depend on:

1. Timing of exposure of hepatotoxic drugs in relation to exposure to HAART.
2. Drugs that both induce and inhibit CYP3A, as well as on the consumption of alcoholic beverages.

MORTALITY OF COINFECTED PATIENTS DUE TO END-STAGE LIVER DISEASE

Cohort	*Year*	*Liver disease mortality rate (%)*	*Risk factor for liver disease*[a]
United States			
Inpatients (66)	1991	11.5	IDU (57%) and alcohol use (35%)
	1996	13.9	IDU (75%) and alcohol use (36%)
	1998–1999	50	IDU (77%) and alcohol use (72%)
Hemophilia patients (69)	1978–1999	12.9	$HBsAg^+$ and alcohol abuse Age of HCV infection
Outpatients, HIV clinic (72)	1995	1.8	Not reported
	1997	20	
	1999	19	
VAMC inpatients (73)	1994–1998	47	HCV infection (IDU)
Spain			
Inpatients (74, 75)	1991–1995	4.8	HCV infection
	2000	45	
France			
Inpatients (76)	1995	1.6	HCV > HBV = alcohol abuse > HBVHCV
	1997	7.8	HCV > alcohol abuse > HBVHCV > HBV
Italy			
Inpatients (77)	1987–1995	12	$HBsAg^+$ and alcohol abuse
	1997–1998	35	

[a]HBVHCV indicates coinfection with hepatitis C and hepatitis B in HIV patients.

Hepatotoxicity Induced by Antiretroviral Agents

- **All antiretroviral agents can cause hepatotoxicity, irrespective of alcohol (some more so than others)**
  - **PIs**
  - **NNRTIs: nevirapine**
  - **NRTIs**
    - **High-risk overall**
      - **Didanosine, stavudine**
    - **High-risk in combination with therapy for hepatitis virus infection**
      - **Didanosine, stavudine, abacavir**
      - **Zidovudine (anemia)**
- **All patients starting HAART should be monitored carefully for hepatotoxicity**

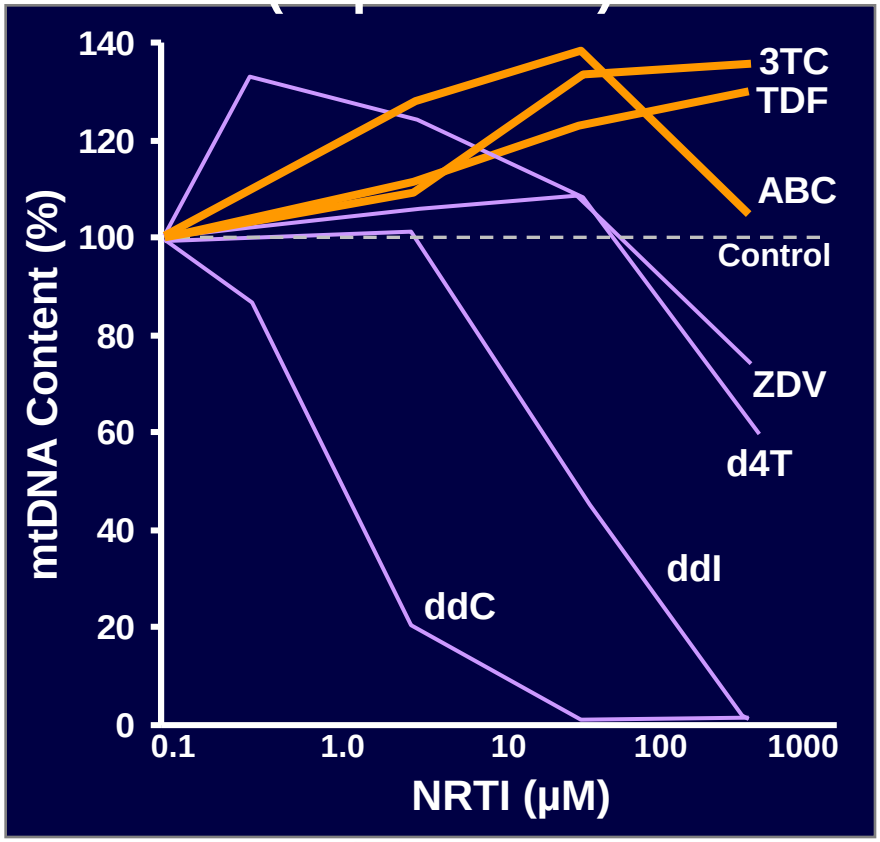
Montessori V, et al. *Semin Liver Dis.* 2003;23:167-172. Alvarez D, et al. *J Viral Hepat*. 2006;13:683-689.Bani-Sadr F, et al. *JAIDS.* 2007;45:123-125.

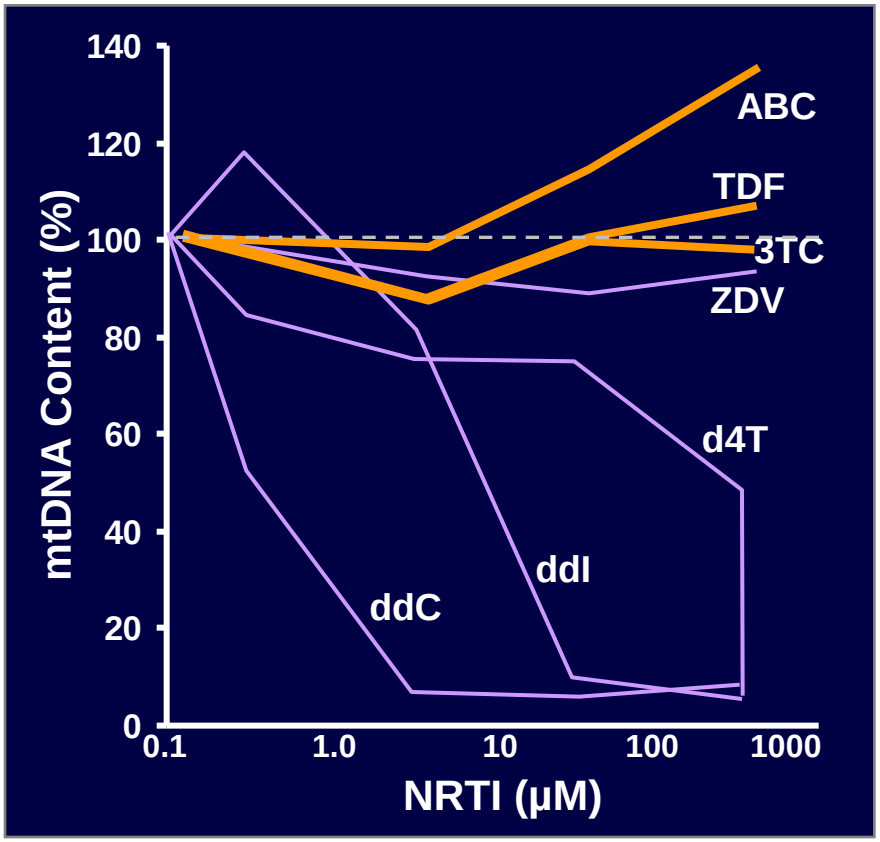
Mechanisms of Liver Injury Induced by Antiretroviral Therapy

- Mitochondrial toxicity
  - NRTIs (especially zidovudine, didanosine, and stavudine)
  - Usually occur after long-term exposure median 9 months
- Hypersensitivity
  - Nevirapine, abacavir
  - Occur early, usually within 6 to 12 weeks
  - Often associated with rash
- Direct toxicity
  - PIs
  - Fatty liver (NAFLD or NASH) caused by insulin resistance
- Immune reconstitution

Nunez M, et al. *Drug Saf.* 2005;28:53-66.
Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision November 3, 2008.

Inhibition of Mitochondrial DNA Content After 9 Days of NRTI Exposure





Birkus G, et al. *Antimicrob Agents Chemother.* 2002;46:716-723.

The Identification and Management of Alcohol Abuse in HIV Patients

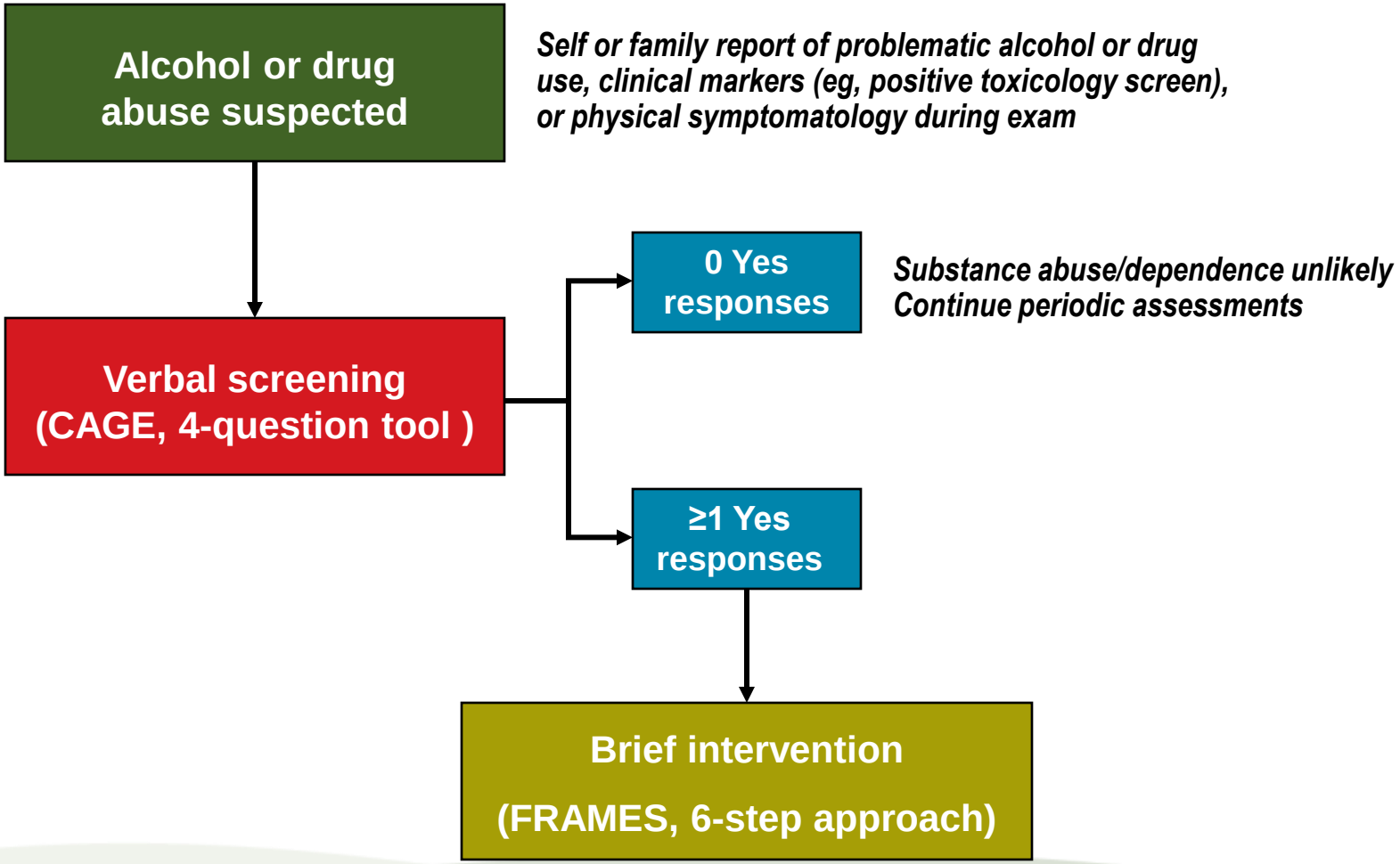
The Identification and Management of Alcohol Abuse Issues in HIV Patients

- Alcohol abuse assessment should be part of the routine medical history in patients who present with HIV.

- All available resources should be employed to stabilize an active alcohol user in preparation for ART initiation:
  - Alcohol abuse treatment is often necessary for successful HIV management.
  - Concurrent psychiatric illnesses should be identified.

Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed March 16, 2009.

Substance Abuse Assessment Algorithm



AIDS Education and Training Centers National Resource Center. Substance Abuse Toolkit. http://aidsetc.org/aidsetc?page=etres-display&resource=etres-310. Accessed March 17, 2009.

CAGE Questionnaire

1. Have you ever felt you should **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)?

CAGE Score	Probability of Abuse or Dependence
0	7%
1	46%
2	72%
3	88%
4	98%

1. Buchsbaum DG, et al. *Ann Intern Med.* 1991;115(10):774-777.
2. Ewing JA. *JAMA*. 1984;252(14):1905-1907.
3. AIDS Education and Training Centers National Resource Center. Substance Abuse Toolkit. http://aidsetc.org/aidsetc?page=etres-display&resource=etres-310. Accessed March 17, 2009.
4. Mersy DJ. *Am Fam Physician.* 2003;67(7):1529-1532.

Brief Intervention: FRAMES

Feedback: Address concerns about use: I'm concerned about how alcohol is affecting your liver" (your work, relationships, mood, behavior)

Responsibility: Emphasize that change is up to patient. "Only you can decide to make your life better. There are programs that can help you."

Advice: Give your specific goals for the patient: "I want you to be evaluated at a treatment center."

Menu: Offer alternatives to advice: "You could go to an AA (or NA) meeting."

Empathy: Listen with empathy: "I imagine talking about this is difficult."

Self-efficacy: Encourage responses that support patient's confidence: "You deserve better – you can be better with help," or "Change can happen, but it takes time."

AIDS Education and Training Centers National Resource Center. Substance Abuse Toolkit. www.aidsetc.org. Accessed March 17, 2009.

Substance Abuse Treatment Programs Are Associated With Improved Adherence to ART

Drug abuse treatment and adherence[a] to ART

HIV Patients in the Women's Interagency HIV Study 1998-2002
N=573

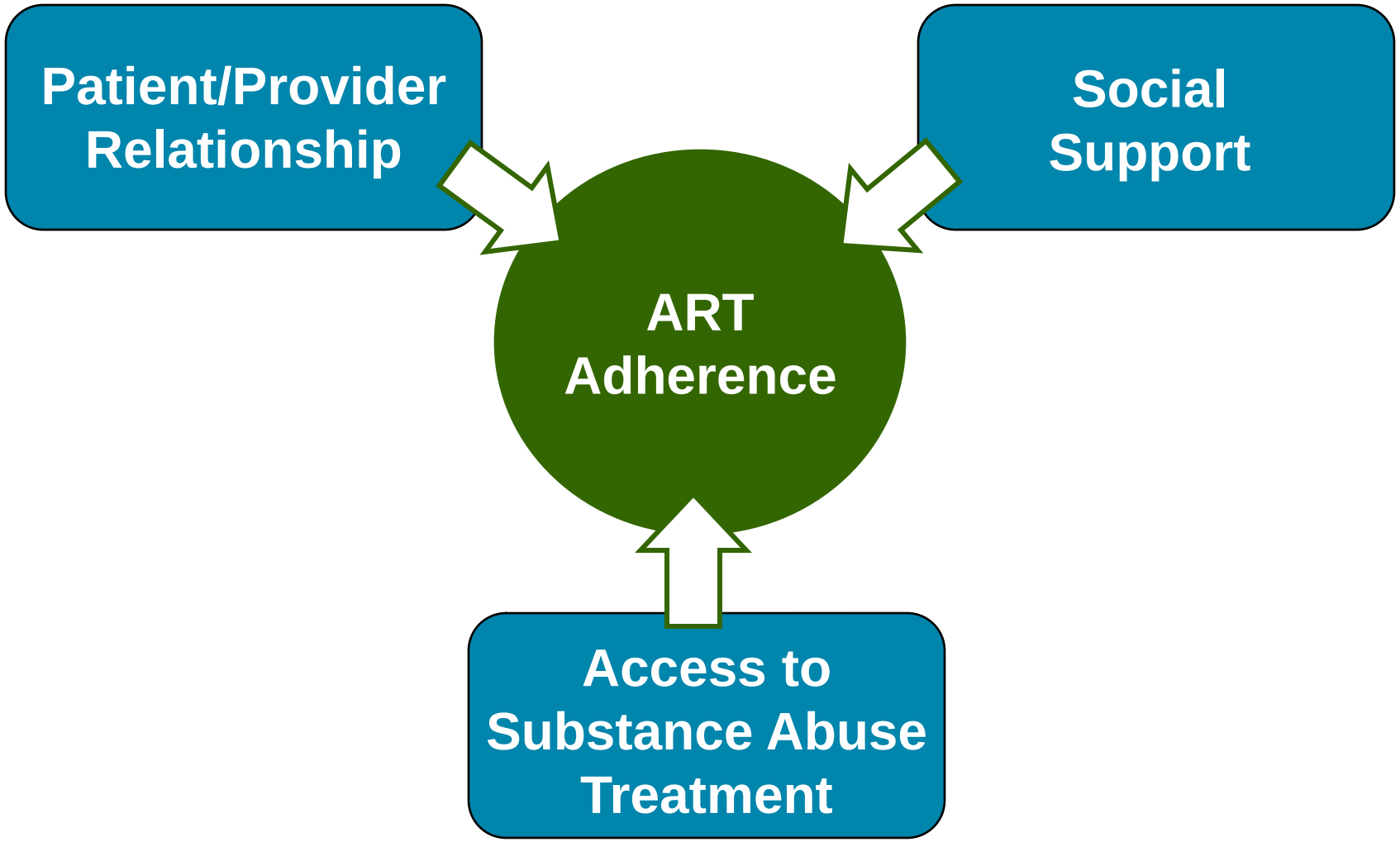
Drug use history/drug abuse treatment type	Adjusted OR (95% CI)
• No drug use/no drug abuse treatment	Reference
• Drug use history/no drug abuse treatment	0.40 (0.27-0.58)
• Substitution-based drug abuse treatment	1.18 (.85-1.65)
• Abstinence-based drug abuse treatment	1.19 (.76-1.84)

[a]Adherence defined as a frequency of ≥95% antiretroviral use.

Kapadia F, et al. *Am J Drug Alcohol Abuse.* 2008;34(2):161-170.

HIV Treatment Considerations in Patients With a History of Alcohol Abuse

Factors That May Promote ART Adherence in Patients with a H/O Substance/Alcohol Abuse



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2. Linsk NL, Bonk N. In: Lynch VJ, ed. *HIV/AIDS at year 2000: A sourcebook for social workers.* Needham Heights, MA: Allyn and Bacon; 2000.

ART Should Not Be Withheld Solely Based on a History of Alcohol Abuse

- Efficacy of antiretroviral medications in alcohol abuses when they are not actively using drugs—is similar to that seen in the broader HIV population
- Patients with a history of prior alcohol abuse have adherence rates similar to users
- Therapeutic failure among HIV-infected patients with substance abuse problems generally correlates with the degree that drug use disrupts their daily activities

US Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed March 16, 2009.

Readiness to Initiate ART in Patients With History of Alcohol Abuse

- The clinician should discuss readiness prior to ART initiation because poor adherence can lead to resistance development and possible consequent treatment failure.
- The assessment of readiness should be based on the patient's level of commitment and understanding of:
  - The daily and long-term requirements of the regimen.
  - A plan for integrating treatment into his/her life.
  - The importance of adherence.

Levensky ER. Adherence to HIV treatments. In: *Promoting treatment adherence: a practical handbook for health care providers*. O'Donahue WT, Levensky ER, eds. Thousand Oaks, CA: Sage Publications; 2006.

Considerations in ART Regimen Selection

- Dosing frequency and complexity
- Potential side effects
- Patient perception of drug efficacy
- Lifestyle change required for compliance
- Drug interactions

1. Linsk NL, Bonk N. Adherence to treatment as social work challenges. In: Lynch VJ, Ed. *HIV/AIDS at year 2000: A sourcebook for social workers,* Needham Heights, MA: Allyn and Bacon;2000.
2. US Department of Health and Human Services**.** Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed March 16, 2009.

Summary

- Impact of ethanol abuse on HIV
- Pharmacogenomics and Pharmacogenetics
- Principal consequences of genetic polymorphism and drug metabolizing enzymes
- Biotransformation of drugs and alcohol
- Hepatotoxicity Induced by Antiretroviral Agents
- The Identification and Management of Alcohol Abuse in HIV Patients
- Treating HIV in patients with ethanol abuse

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