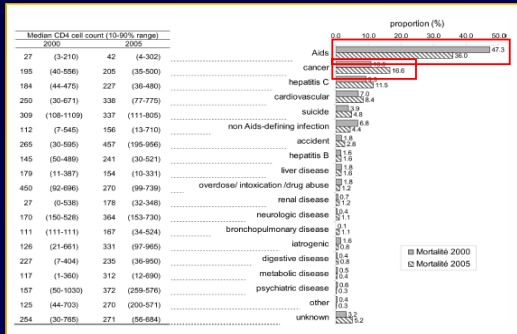


Cancer and HIV— A Patient Case Approach to Drug-Drug Interactions

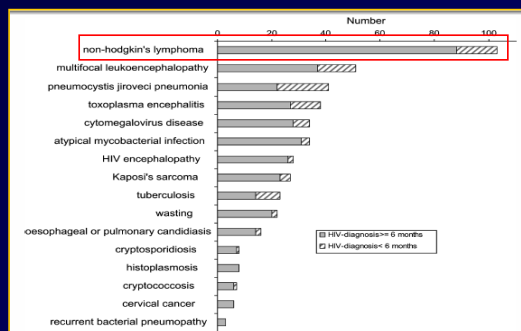
Patricia Pecora Fulco, Pharm.D., BCPS, FASHP
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 Clinical Associate Professor of Pharmacy
 Clinical Assistant Professor of Internal Medicine/
 Division of Infectious Diseases
 Virginia Commonwealth University
 Virginia Commonwealth University Medical Center

Causes of Death: HIV-infected Adults



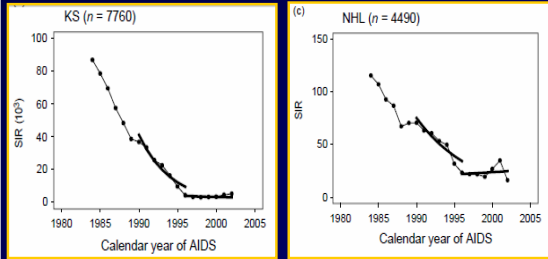
Lewden, C, et al. J Acquir Immune Defic Syndr 2008;48:590-8.

Causes of Death: HIV-infected Adults



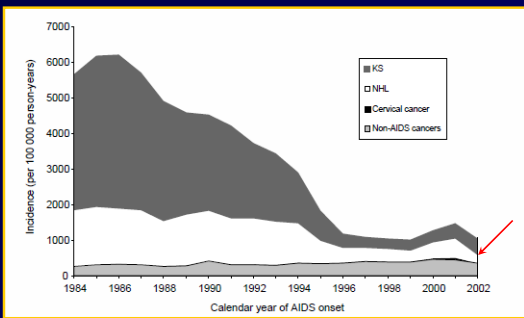
Lewden, C, et al. J Acquir Immune Defic Syndr 2008;48:590-8.

Trends in Cancer Risk Among People with AIDS in the US: 1980-2002



Engels EA, et al. AIDS 2006;20:1645-54.

Trends in Cancer Risk Among People with AIDS in the US: 1980-2002



Engels EA, et al. AIDS 2006;20:1645-54.

Patient Case

- 55yo WM new diagnosis of HIV
 - New symptoms of the following:
 - Nausea
 - Vomiting
 - Abdominal pain
 - R eye pain/periorbital swelling
 - Weight loss
 - Abdominal/pelvic CT
 - Retroperitoneal and mesenteric carcinomatosis
 - Excisional inguinal lymph node biopsy
 - Diffuse large B-cell lymphoma

Patient Case

- Hematology/oncology consultation
 - Consult Infectious Diseases for HAART initiation
 - To initiate CHOP-based chemotherapy

Chemotherapeutic Response and HAART

HAART and Chemotherapeutic Response in AIDS-related Lymphomas

- 27-month longitudinal analysis
 - NHL
 - HIV
- To receive CHOP or CHOP-like regimen
- HAART included:
 - PI or NNRTI-based
 - Two NRTIs
- Primary outcome:
 - To determine the response/survival rate in patients responding to HAART

HAART and Chemotherapeutic Response in AIDS-related Lymphomas

- N=44
 - 36 patients receiving HAART
 - Primarily PI-based (indinavir/nelfinavir/ritonavir)
 - 71% with CR had a virological HAART response [OR 5.6; (95% CI 1.54-20.78)]
- No tolerability differences between HAART responders and non-responders

Antinori A, et al. AIDS 2001;15:1483-91.
Vascher E, et al. Cancer 2001;91:155-63.

Which HAART to Start?

- Comorbid conditions
- Baseline genotypic analysis
- Pharmacogenomic analysis

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, December 1, 2009. www.aidsinfo.nih.gov

Patient Case

- High risk of tumor-lysis syndrome
- Genotypic analysis:
 - Pan-sensitive interpretation
 - L63P
 - V77I
 - I93L
- Pharmacogenomic analysis:
 - HLA-B*5701 (-)

Which HAART to Start?

- Comorbid conditions
- Baseline genotypic analysis
- Pharmacogenomic analysis
- Adherence
- Resistance prediction
- Drug Interactions
- Expected toxicities

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Patient Case

- Normal renal and hepatic function
- Medications
 - TMP/SMX (developed rash)
 - Atovaquone 1500 mg daily

Preferred HAART Regimens

Panel's Recommendations:

- The Panel recommends initiating antiretroviral therapy in treatment naive patients with 1 of the following 3 types of regimen:

- NNRTI + 2 NRTI
- PI (preferably boosted with ritonavir) + 2 NRTI
- INSTI + 2 NRTI

- The Panel recommends the following as preferred regimens for treatment naive patients:

- Efavirenz + tenofovir + emtricitabine (AI)
- Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)
- Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)
- Raltegravir + tenofovir + emtricitabine (AI)

- A list of Panel recommended alternative and acceptable regimens can be found in [Table 5a](#).

- Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.

- Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.

INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; PI = protease inhibitor

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Patient Case

- Hematology/oncology consultation
 - Consult Infectious Diseases for HAART initiation
 - To initiate CHOP-based chemotherapy

Antiretroviral/Antineoplastic Interactions

REVIEW ARTICLE

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Interactions Between Antiretrovirals and Antineoplastic Drug Therapy

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3 Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

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CHOP Elimination

- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisone

CHOP and HAART Elimination

- Cyclophosphamide
 - CYP 2B6
 - CYP 2C19
 - CYP 3A4
- HAART and CYP 2B6
 - Efavirenz
 - Nelfinavir
 - Ritonavir
- HAART and CYP3A4
 - All Protease Inhibitors
 - All Non-Nucleoside Reverse Transcriptase Inhibitors

Antoniou T, Tseng AL. Clin Pharmacokinet 2005;44:111-45. Ranner L, et al. J Clin Oncol 2001;19:1711-8.

CHOP and HAART Elimination

- Doxorubicin
 - Aldoketoreductase enzyme
 - Inactive metabolite—doxorubicinol
 - Inactive metabolites—NADPH-dependent cytochrome reductase
 - Possible CYP—free radical

Antoniou T, Tseng AL. Clin Pharmacokinet 2005;44:111-45. Ranner L, et al. J Clin Oncol 2001;19:1711-8. Toffoli G, et al. Ann Oncol 2004;15:1805-9.

CHOP and HAART Elimination

- Vincristine
 - CYP 3A5
 - Biliary clearance via p-glycoprotein
- 39yo HIV+ male
 - New diagnosis of Burkitt's lymphoma
 - Cyclophosphamide
 - Doxorubicin
 - Methotrexate
 - Vincristine
- Lopinavir/ritonavir with 2 NRTIs

Antoniou T, Tseng AL. Clin Pharmacokinet 2005;44:111-45. Leveque D, et al. Pharm World Sci 2009;E-pub ahead of print 13.

Which HAART to Start?

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- Baseline genotypic analysis
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- Adherence
- Resistance prediction
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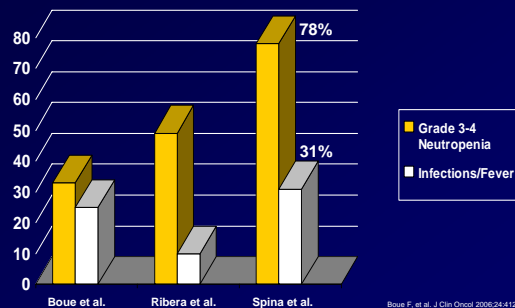
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, December 1, 2009. www.aidsinfo.nih.gov

CHOP and HAART Toxicities

- AIDS-related lymphomas (N=218)
- Chemotherapeutic regimens:
 - CHOP
 - Rituximab with CHOP
 - Cyclophosphamide, doxorubicin, etoposide (CDE)
 - Rituximab with CDE
- Protease-inhibitor based HAART (N=161)
 - Zidovudine excluded (N=80)
 - Zidovudine and/or ritonavir excluded (N=42)
- End-stage AIDs excluded (N=56)

Boue F, et al. J Clin Oncol 2006;24:4123-8.
Spina M, et al. Blood 2005;105:1899-7.
Ribera J-M, et al. Br J Haematol 2008;140:411-9.

CHOP and HAART Toxicities



Boue F, et al. J Clin Oncol 2006;24:4123-8.
Spina M, et al. Blood 2005;105:1899-7.
Ribera J-M, et al. Br J Haematol 2008;140:411-9.
Spina M, et al. J Clin Oncol 2007;25:47.

Chemotherapy and HAART Toxicities

- Chelsea and Westminster cohort (N=46)
 - HIV-positive and
 - AIDS-related lymphoma diagnosed 1999-2003

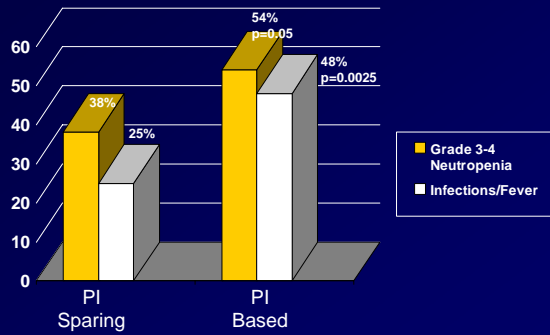
Bower M, et al. Blood 2004;104:2943-6.

Chemotherapy and HAART Toxicities

- Concomitant HAART
 - PI-based: 11 patients (one patient on zidovudine)
 - PI with 2 NRTIs (N=9)
 - NNRTI with PI and NRTIs (N=2)
 - PI-sparing: 35 patients (11 patients on zidovudine)
 - Triple NRTI (N=3)
 - NNRTI with 2 NRTIs (N=32)

Bower M, et al. Blood 2004;104:2943-6.

Chemotherapy and HAART Toxicities



Bower M, et al. Blood 2004;104:2943-6.

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Integrase Inhibitor: Raltegravir (Isentress)

- Novel MOA
- Dosage: 400 mg bid
- Elimination:
 - Metabolism: glucuronidation via UGT
- Drug Interactions
 - Atazanavir (increases RAL by 70%)
 - Efavirenz (decreased RAL by 36%)
 - Ritonavir (no effect)
 - Tipranavir/Ritonavir (decreased RAL by 24%)
- Adverse events

Ginsberg B, et al. Lancet 2007;369:1261-9. Raltegravir Prescribing Information. www.fda.gov. Markowitz M, et al. J Acquir Immune Defic Syndr 2008; 58:1000-1006. Ju, et al. Lancet August 3, 2009.

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Alternative HAART Regimens

Alternative Regimens (Regimens that are effective and tolerable but h
An alternative regimen may be the preferred regimen for some patients.)

NNRTI-based Regimens (in alphabetical order)

- EFV + (ABC or ZDV)/3TC¹ (BI)
- NVP + ZDV/3TC¹ (BI)

PI-based Regimens (in alphabetical order)

- ATV/r + (ABC or ZDV)/3TC¹ (BI)
- FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI)
- LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI)
- SQV/r + TDF/FTC¹ (BI)

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, December 1, 2009.
www.aidsinfo.nih.gov
Sax PE, et al. N Engl J Med 2009;361:253-60.

Patient Case

- Hematology/oncology consultation
 - Consult Infectious Diseases for HAART initiation
 - Raltegravir 400 mg twice daily
 - Abacavir 600 mg/Lamivudine 300 mg once daily

Patient Case

Time (months)	Total WBC count	Absolute Lymph count	Absolute CD4 count (cells/mm ³)	Percent CD4 (%)	Viral Load (copies/mL)
Baseline	2.3 x 10 ⁹	0.6 x 10 ⁹	36	6	18.7 x 10 ³
Three	0.5 x 10 ⁹	Unable to report	119	7	< 48
Four	3.6 x 10 ⁹	0.6 x 10 ⁹	48	8	< 48
Seven	1.4 x 10 ⁹	0.2 x 10 ⁹	20	10	< 48
Eight*	1.0 x 10 ⁹	0.5 x 10 ⁹	40	8	13 x 10 ³
Ten	1.3 x 10 ⁹	0.3 x 10 ⁹	21	7	901
Twelve	1.6 x 10 ⁹	0.4 x 10 ⁹	20	5	95

*Patient discontinued antiretrovirals for three weeks prior to this evaluation.

Fukuo PF, et al. Raltegravir-based HAART in a patient with large B-cell lymphoma. Ann Pharmacother 2010. (fearnaia.com, DOI:10.1345/aph.1M370).

Questions