Disclosure

• Dr. Blaszczyk
  – Serves on the educational advisory board of GeriatricPharmacyReview.com
  – Provides updates to monographs for Omnicare Formulary

• Dr. Duval
  – Nothing to disclose
Objectives

By the end of the presentation, the audience should be able to:

– Describe the epidemiology of HIV infection in older adults, as well as the pathophysiology of HIV

– Recognize agents utilized for the treatment of HIV, mechanisms of action, relevant side effects and important monitoring within the older population

– Discuss guidelines for the treatment of HIV, as well as the HIV and Aging Consensus project and literature supporting specific interventions for HIV in the older population

– Design a therapeutic and monitoring plan for a senior patient with HIV, as well as education in regards to decreasing the transmission of the disease and the laws, including Florida’s, surrounding this
The Alphabet-Soup of HIV

- HIV – Human Immunodeficiency Virus
- AIDS – Acquired Immunodeficiency Syndrome
- HAART – Highly-active Antiretroviral Therapy
- ART – Antiretroviral Therapy
- NRTI – Nucleos(t)ide Reverse Transcriptase Inhibitor
- NNRTI – Non-nucleoside Reverse Transcriptase Inhibitor
- PI – Protease Inhibitor
“New Phenomenon”

• By the year 2015, an estimated 50% of Americans infected with HIV will be over 50 years of age

• New HIV infections: ~15% ≥ 50 years of age
  – Risk behaviors in the elderly
    • Perceived risk
    • Lack of knowledge

HIV Infection: A Chronic Disease State

- Increased survival due to HAART
- Older population
  - Increased number of co-morbid disease states
    - Cardiovascular disease
    - Diabetes
    - Chronic kidney disease
    - Depression
    - Dementia
  - Increased number of medications
- Medication Adherence

Physiological Changes in the Elderly

- Increased risk of HIV progression
  - Thymus involution by age 50
    - Slower regeneration of CD4+ T cells
    - Inhibition of CD4+ T cell function
- Decline in renal function
- Decline in hepatic function
- Frailty
- Chronic inflammation
- Decline in bone mineral density

HIV Infection

• HIV
  – Retrovirus (enveloped RNA virus)
• Depletion of CD4+ T lymphocytes
  – Decreased half-life of CD4+ T lymphocytes
  – Impaired production of CD4+ T lymphocytes
• Impaired cell-mediated immunity
  – Opportunistic infections
  – Malignancy

Opportunistic Infections Associated with HIV

- Candidiasis
- *Pneumocystis jirovecii* pneumonia (PCP)
- *Toxoplasma gondii* encephalitis
- *Mycobacterium avium* complex (MAC) disease
- Cytomegalovirus
- Herpes simplex virus
- Histoplasmosis
Malignancies Associated with HIV

- Kaposi’s sarcoma
- Non-Hodgkin’s lymphoma
- Cervical cancer

Drug Targets

Entry Inhibitors

1. Fusion of HIV to the host cell surface.

2. RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.

Integrate Inhibitors

NRTIs, NNRTIs

Fusion Inhibitors

Protease Inhibitors

3. Viral DNA is formed by reverse transcription.

4. Viral DNA is transported across the nucleus and integrates into the host DNA.

5. New viral RNA is used as genomic RNA and to make viral proteins.

6. New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.

7. The virus matures by protease releasing individual HIV proteins.


Last Updated April 03, 2012
Nucleoside Reverse Transcriptase Inhibitors

• NRTIs
  – Abacavir
  – Didanosine
  – Emtricitabine
  – Lamivudine
  – Stavudine
  – Zidovudine
  – Lamivudine/Zidovudine
  – Abacavir/Lamivudine/Zidovudine
  – Abacavir/Zidovudine
  – Emtricitabine/Efavirenz/Tenofovir
  – Tenofovir
  – Tenofovir/emtricitabine

NRTIs Mechanism

• NRTIs:
  – Nucleoside analogs (contains nitrogenous base and deoxyribose)
  – Nucleotide analogs (also contains phosphate group)
    • Competitive inhibition of HIV-1 reverse transcriptase
    • Incorporated into replicating DNA strand
    • Lack 3-hydroxyl group → inability of subsequent nucleotides to attach to DNA strand → termination of replication

# NRTIs Adverse Effects and Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effects</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td><strong>Hypersensitivity reactions</strong>, lactic acidosis, hepatomegaly/steatosis, N/V/D, malaise</td>
<td>HLA-B*5701 testing</td>
</tr>
<tr>
<td>Didanosine</td>
<td><strong>Pancreatitis, peripheral neuropathy, lactic acidosis</strong>, hepatomegaly/steatosis, diarrhea,</td>
<td>Renal function</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Lactic acidosis, hepatomegaly/steatosis</td>
<td>Renal function</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Headache, N/V/D, peripheral neuropathy, lactic acidosis</td>
<td>Renal function</td>
</tr>
<tr>
<td>Stavudine</td>
<td><strong>Peripheral neuropathy, lipodystrophy, dyslipidemia</strong>, headache, lactic acidosis</td>
<td>Renal function, liver function, lipids</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td><strong>Severe peripheral neuropathy, pancreatitis, lactic acidosis</strong>, stomatitis/oral ulcers</td>
<td>Renal function</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>N/V, headache, malaise, <strong>neutropenia, macrocytic anemia</strong>, lactic acidosis</td>
<td>Renal function</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Renal toxicity, decreased bone mineral density, lactic acidosis</td>
<td>Renal function, BMD</td>
</tr>
</tbody>
</table>

Non-nucleoside Reverse Transcriptase Inhibitors

• NNRTIs
  – Delavirdine
  – Efavirenz
  – Etravirine
  – Nevirapine
NNRTIs Mechanism

• NNRTIs
  – Bind to allosteric binding site (non-active binding site) on reverse transcriptase
    • Induces conformational change in reverse transcriptase active binding site
      – Inhibition of reverse transcriptase function

NNRTIs Adverse Effects and Monitoring

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<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rash, headache, diarrhea, elevated LFTs</td>
<td>Liver function, drug-drug interactions</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rash, dizziness, insomnia, nightmares, psychosis, hepatotoxicity</td>
<td>Liver function, drug-drug interactions</td>
</tr>
<tr>
<td>Etravirine</td>
<td><strong>Severe skin rash</strong>, nausea</td>
<td>Liver function</td>
</tr>
<tr>
<td>Nevirapine</td>
<td><strong>Severe hepatotoxicity</strong>, rash (SJS, TENS)</td>
<td>Liver function</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Rash, <strong>elevated LFTs</strong>, dyslipidemia, nausea</td>
<td>Lipid panel, liver function</td>
</tr>
</tbody>
</table>

Protease Inhibitors

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir/Ritonavir

- Ritonavir
- Nelfinavir
- Saquinavir
- Tapranavir

Protease Inhibitors Mechanism

- PIs:
  - HIV protease:
    - Cleaves newly synthesized polyproteins to create mature proteins
  - Inhibition of HIV protease $\rightarrow$ inhibition of maturation of HIV $\rightarrow$ HIV unable to replicate

PI Adverse Effects and Monitoring

• Class adverse effects
  – Metabolic adverse effects
    – Dyslipidemia
      » Changes in lipid metabolism: Increase levels of VLDL (carrier of triglycerides)
    – Hyperglycemia/insulin resistance
      » Inhibition of glucose transporters, inhibition of adipocyte differentiation, and induction of adipocyte apoptosis
  – Monitoring
    – Lipid panel, serum glucose

# PI Adverse Effects and Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Additional Adverse Effects</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td><strong>Hyperbilirubinemia</strong>, headache, bradycardia</td>
<td>Liver function, heart rate, glucose, lipid panel, drug-drug interactions</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Skin rash, <strong>hepatitis</strong>, bleeding</td>
<td>Liver panel, drug-drug interactions (avoid in sulfa-allergic patients)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Rash, bleeding</td>
<td>Lipid panel, (caution in sulfa-allergy)</td>
</tr>
<tr>
<td>Indinavir</td>
<td><strong>Hyperbilirubinemia</strong>, nephrolithiasis, alopecia</td>
<td>Liver function, lipid panel, blood glucose</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Nausea, headache</td>
<td>Liver panel, drug-drug interactions</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>N/V/D, <strong>elevated LFTs</strong></td>
<td>Liver panel, lipid panel, blood glucose</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>N/V/D, asthenia</td>
<td>Lipid panel, drug-drug interactions</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>N/V/D, <strong>indigestion</strong></td>
<td>Lipid panel (avoid rifampin)</td>
</tr>
<tr>
<td>Tipranavir</td>
<td><strong>Elevated LFTs</strong>, bleeding</td>
<td>Liver panel, lipid panel, glucose</td>
</tr>
</tbody>
</table>

Fusion Inhibitors

• Enfuvirtide

• Mechanism
  – Binds to gp41 (viral protein) preventing viral embedding and formation of entry pore on host cell

• Adverse Effects
  – Injection site reactions, respiratory infections, fatigue, peripheral neuropathy, N/V/D, pancreatitis

• Monitoring
  – Signs and symptoms of pneumonia

Entry Inhibitors

- Maraviroc
- Mechanism
  - Selective, reversible antagonist
  - Blocks interaction between CCR5 and gp120 (viral protein)
- Adverse Effects
  - Hepatotoxicity, eosinophilia, rash, orthostasis, increased risk for cardiovascular events
- Monitoring
  - Liver function, renal function, CBC, drug-drug interactions

Integrase Inhibitors

• Raltegravir

• Mechanism
  – Prevents integrase insertion needed for processing viral DNA and subsequent integration of viral DNA with host cell DNA

• Adverse effects
  – Nausea, headache, rash, pruritis, fatigue, rhabdomyolysis

• Monitoring
  – Creatine kinase, blood chemistry

HIV Treatment Guidelines
HIV Treatment Guidelines - General

• 2012 Recommendations
  – International Antiviral Society – USA Panel (IAS-USA)
    • Systematically reviewed literature
    • International experts in HIV and clinical care
    • Recommendations made by full-panel consensus
  – Update for those resource-rich settings
  – Published in July 2012

IAS-USA: When to start...

- ART should be offered to all adults with HIV infection, regardless of CD4 count
  - Those 60+, CD4 count never mattered
  - The lower the CD4 count, the better the evidence for starting ART

- Make sure patient can adhere to ART
  - Within nursing facility
  - Community-dwelling
    - What does the rest of their regimen look like?

Why is adherence so important?

• Adherence = Improved outcomes
  – Better viral suppression
    • Good for the patient, and their partner(s)
  – Better immunologic recovery
  – Decreased morbidity and mortality
  – Decreased rates of resistant strains

IRIS

- Immune reconstitution inflammatory syndrome (IRIS)
  - Seen in some as immune function returns
  - Looks like infection
    - Fever
    - Malaise
    - Typical symptoms present with opportunistic infections
  - Lower the CD4+ count to start, the higher the risk
Goals of Therapy

• Lifelong, continuous suppression of HIV replication
• Decrease emergence of resistance
• Help with immune recovery
• Improve health & quality of life
  – Pill burden!
• Minimize side effects and drug-drug interactions
IAS-USA: What to start?

- Treatment-naïve Patients
- 2 NRTIs + Potent 3rd agent
  - NNRTI
  - Ritonavir-boosted PI
  - Integrase-strand transfer Inhibitor

NRTIs + NNRTI

• **Recommended regimens**
  - Efavirenz/tenofovir/emtricitabine
  - Efavirenz + abacavir/lamivudine

• **Alternative regimens**
  - Nevirapine + tenofovir/emtricitabine
  - Nivirapine + abacavir/lamivudine
  - Rilpivirine/tenofovir/emtricitabine

NRTIs + PI

• Recommended regimens
  – Darunavir/ritonavir + tenofovir/emtricitabine
  – Atazanavir/ritonavir + tenofovir/emtricitabine
  – Atazanavir/ritonavir + abacavir/lamivudine

• Alternative regimens
  – Darunavir/ritonavir + abacavir/lamivudine
  – Lopinavir/ritonavir + tenofovir/emtricitabine
  – Lopinavir/ritonavir + abacavir/lamivudine

NRTIs + Integrase strand transfer inhibitors

• Recommended regimen
  – Raltegravir + tenofovir/emtricitabine

• Alternative regimen
  – Raltegravir + abacavir/lamivudine

Treatment-experienced

• Initial virologic failure
  – HIV-1 RNA > 50 copies/mL – confirm with another test in 2-4 weeks
  – Send for genotypic resistance testing
• For all those with initial virologic failure, will switch to 3 new, active agents

NRTIs + NNRTI Failure

- NNRTI resistance can be present, so delays in switching should be avoided
- Can use:
  - NRTIs + ritonavir-boosted PI
  - NRTIs + Integrase strand transfer inhibitors

Other Failures

• Initial PI-based Regimen
  – Resistance to PIs is rare
  – Potential regimens:
    • Likely will need to switch out one of the NRTIs (resistance-testing will tell you which)
    • Could use NNRTI
    • Switch to a new NRTI-based therapy, could switch to another PI, but probably don’t need to (Darunavir has best evidence)

Other Failures

• Integrase strand transfer inhibitor-based
  – Cross-resistance seen between 2 available agents
  – Seek out new 3-active drug regimen from other types

Monitoring

• HIV-1 RNA levels ("Virologic response")
  – At least every 3 months after any initiated treatment or change of therapy
  – Once suppressed for 1 year, can go up to 6 months
  – Goal: < 50 copies/mL

• CD4 count ("Immunologic response")
  – At least every 3 months after initiated therapy
  – If stable > 350/mcL for 1 year, can go up to 6 months
  – If < 200/mcL, will need primary opportunistic infection prophylaxis

The HIV and Aging Consensus Project: Now what do I do with this?!
HIV & Aging Project

• AGS, AAHIVM and AIDS Community Research Initiative of America
• 14 member panel
  – 7 geriatrics-specialists and 7 HIV-specialists
  – Used modified Delphi technique for recommendations
• Older = 50 +

• Treatment strategies
  – Not guidelines
  – Consensus opinions

HIV & Aging Project

• Utility and futility of interventions needs to be assessed
  – HIV viewed as a chronic disease
  – No longer a death sentence
    • Long-term goals of care need to be considered
    • Long-term sequelae of uncontrolled diseases need to be considered
  – However, life-expectancy and functional status must still be taken into consideration

• Addresses the management of co-morbid conditions, and special monitoring considerations
Screening, Initiating & Monitoring therapy

• Screening
  – Opt-out HIV screening on all adults

• Initiating
  – Broken down by CD4 count
  – IAS-USA – all people regardless of CD4 count
  – If possible, avoid PIs in those with DM Type 2 or hyperinsulinemia

• Monitoring
  – Suggest following IAS-USA guidelines for monitoring

CV, DM Type 2, HIV and Aging

- Smoking cessation
- Lipid goals
  - Continue to use ATPIII guidance and Framingham Risk Assessment
  - If on a PI, will definitely need lipid management
- Avoid excessive weight gain
- DM Type 2
  - Screen as per usual, both before and during ART, using A1c
  - Increased A1c goal of 8% for frail adults

Renal function

• Annually
  – Serum creatinine
  – eGFR
  – Urine protein
  – Changes in kidney function should be addressed by a specialist

• Renal adjustment of many ART medications is necessary
Hypertension

- Adhere, if possible, to non-pharmacologic interventions for HTN
- Use recommended guidelines for HTN (JNC 7)
  - No lower than 130/70
- Consider use of ACE Inhibitor or ARB
- Start low and go slow with BP meds
Drug-Drug Interactions & Polypharmacy

• Encourage medication reconciliation & a medication review
• Encourage use of one pharmacy, with HIV specialty if available
• Drug dosing
  – Use Cockcroft-Gault for renal dosing
  – Check liver panel

Hepatitis & Cancer Screening

• Hepatitis
  – All HIV-infected individuals screened for HAV, HBV and HCV
  – Rescreen for these with any unexplained liver enzyme elevations

• Cancer
  – Use general population guidelines, unless HIV-specific guidelines exist
    • Cervical, anal and liver cancer

COPD & Immunizations

• COPD
  – Follow management guidance for general population
  – GOLD COPD guidelines

• Immunizations
  – At higher risk for vaccine-preventable diseases
  – Use CDC tables
    • Change every year
    • For those severely immunocompromised, don’t recommend MMR, Zoster or Varicella

Sexual Health

• Screen for high-risk sexual behavior and STDs
  – Talk about safe-sex practices
• Stress adherence to therapy
  – Decrease risk for transmission
• Use sexual dysfunction medications along with education

Osteoporosis

- Screen for osteoporosis
  - Impact of ART
  - Aging bones
- Screen for vitamin D deficiency
  - Impact of ART

Psychiatric Issues

• Screening for cognitive dysfunction and depression important
  – GDS

• Anxiety
  – Use SSRIs first line and non-benzos for long-term management
  – If a benzo is needed, short or intermediate acting are most preferred
    • Lorazepam

• Counsel on alcohol and substance abuse

Advanced Directives

• Advanced care planning advised
  – Durable Power of Attorney for health care
  – Advanced Directive
Resources

• AIDS Info Clinical Guidelines Portal
  – http://www.aidsinfo.nih.gov/guidelines/

• American Academy of HIV Medicine HIV and Aging Page
  – http://www.aahivm.org/hivandagingforum
Patient Case

• 71-year old WM living in independent-living area of CCRC

• Past sexual history of sexual relations with men
  – Partner of 30-years passed away 5-years ago
  – Has been sexually active with many partners for the past 3 years
  – Consents to HIV test given history at primary care clinic visit

• Tests positive for HIV
Patient Case

• PMH
  – Dyslipidemia
  – Osteoarthritis
  – HTN
  – Depression

• PSH
  – Hiatal hernia repair 2009
Patient Case

- Current medications
  - Simvastatin 40 mg orally at bedtime
  - Atenolol 100 mg orally in the morning
  - HCTZ 25 mg orally in the morning
  - Celecoxib 200 mg orally in the morning
  - Sertraline 100 mg orally in the morning
  - ASA 81 mg orally at bedtime
  - Senior MVI 1 tablet orally daily
Patient Case

• Labs
  – TC 123  LDL-C 56  HDL 45  TGs 110
  – Chem 7 WNL
  – Liver panel WNL
  – WBC 7.1
  – H/H 13.1/39.6
  – Platelets 192
  – 25-OH Vitamin D 31

• HIV Labs
  – CD4+ count – 240 cells/mL
  – HIV-RNA -> 100,000 copies/mL
Patient Case

• BPs
  – Home log
    • Avg AM 120/65 Pulse AM 61
    • Avg PM 131/89 Pulse PM 67

• PE
  – Non-contributory

• Subjective
  – “Other than feeling a little worn down, I feel pretty good for an old guy!”
Case Questions

• What interventions can we recommend for him?
  – ART to start today!

• What to start?
  – 2 NRTIs + NNRTI
  – 2 NRTIs + ritonavir-boosted PI*
  – 2 NRTIs + Integrase-strand transfer inhibitor
Case Questions

• The MD decides to start 2 NRTIs + ritonavir-boosted PI
  – Atazanavir 300 mg + Ritonavir 100 mg + Emtricitabine 200 mg/Tenofovir 300 mg orally daily
  – 3 separate drugs
  – Once-daily regimen
Case Questions

• What drug interactions exist and what interventions must be made?
  – Ritonavir + Atazanavir + Simvastatin
    • Need to change lipid lowering agent
  – Ritonavir + Atazanavir + MVI
    • Calcium in MVI could decrease absorption
    • Separate administration
  – Atazanavir + Atenolol
    • Increased monitoring of BP and pulse
Case Questions

- What additional monitoring should be undertaken upon start of ART?
  - EKG
    - QTc prolongation – ritonavir, atazanavir, sertraline
  - Baseline renal function, liver and lipid panels, blood glucose (A1c)
  - Baseline CD4+ and HIV-1 RNA levels
  - DXA
  - Adherence
Case Questions

• When should we recommend follow-up?
  – Labs
    • HIV-1 RNA and CD4+ at least every 3 months
      – Can go to Q6 months once HIV-1 RNA suppressed to undetectable and CD4 count is > 350/mcL for 1 year
    • Chem panel, Liver panel every 3 months
    • Lipids every 6 months
  – Imaging
    • Follow-up DXA in 2 years
  – EKG
    • With any dosage or regimen change
Case Questions

• What patient education will we need to provide to this newly diagnosed individual?
  – Adherence to therapy
  – Limit alcohol consumption and stop smoking
  – Maintain all lab and follow-up appointments
  – Legal issues
    • Knowingly transmitting HIV
    • Florida 384.24
Wrapping up…

• The older individual with HIV is becoming more common
  – How long before you see one in your facilities?
• Senior-care pharmacists will be called upon to help manage this population
• HIV and the aging population will be a rapidly expanding area of research
References


References


