Case #1

**HPI:** 58 yo Caucasian woman presented to my clinic Aug 2006 with 4-5 years of cognitive decline – from employed as printer to sporadic homelessness, all thought 2° profound depression. Admitted to UCSF inpatient psychiatric unit 7/06
Case

- **PMH**: significant for Non-Hodgkin’s lymphoma dx’d 8 years previously treated with CHOP (had PCP PNA, CMV PNA, & disseminated VZV in context of chemo) and in remission since. Has had multiple episodes of bacterial pneumonias since and progressive affect loss, cognitive decline, failure to care for self, depression

Case

- **MEDS**: Multiple psych meds
- **ALL**: NKDA
- **SHx**: No smoking; social EtOH; occasional MJ; no IVDU or other drugs; sex with men only (3 sexual partners in last 20 years); educated and successful woman in printing and journalism prior to decline
- **FHx**: Noncontributory
**Case**

**PE:** 130/70; 92%RA; 37.0; 110; 22
Thin, white woman NAD; Somnolent, flat affect, would track, but sits with dazed expression and answers questions slowly; only oriented to self; can follow 1-step, but not 2-step commands; poor effort on neuro exam, but no clear focal deficits; flexor plantar response; no thrush; RRR S1 S2 no mgr; clear lungs; abdomen soft; no peripheral edema or rash

**LABS:** WBC 5.6; Hct 34.2; Plt 316; SPEP – general increase in gamma region suggestive of polyclonal gammopathy; ESR 46; lytes, LFT's unremarkable

**CXR:** Increased lung markings in a nodular-reticular pattern; **Head CT:** Parenchymal loss; periventricular white matter T2 prolongation nonspecific
Diagnosis?

- *Pneumocystis jiroveci* on bronch
- HIV Ab positive
- CD4 46 (6%) with viral load >500,000 copies/mL
- Probable HIV encephalopathy (PML and CMV ruled out) causing progressive (and preventable) cognitive decline
- Now. . Improving gradually on HIV therapy, but residual organic brain damage

¼ of HIV-infected people in U.S. unaware of infection status

| People living with HIV/AIDS                           | 1,039,000 to 1,185,000 |
| Percent unaware of HIV status                        | 24% to 27% (>250,000)   |
| Relative risk of transmission from unaware patient compared to aware | 3.5 times |

Women may be less likely to identify risk for HIV (WIHS)

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous drug use</td>
<td>34%</td>
<td>10%</td>
</tr>
<tr>
<td>Heterosexual risk</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>Transfusion risk</td>
<td>4%</td>
<td>--*</td>
</tr>
<tr>
<td>No identified risk</td>
<td>20%</td>
<td>48%</td>
</tr>
</tbody>
</table>

* Transfusion risk not assessed in 00/01 cohort


"Late Testers” Account for Almost 40% of HIV Diagnoses

Risk factors for later presentation and OI’s: racial/ethnic minority, no perceived risk factors, older age²

Epidemic in women skewed towards minorities

HIV/AIDS among U.S. women

- Hispanic: 14%
- Other: 1%
- White: 17%
- African-American: 68%

HIV/AIDS among U.S. men

- Hispanic: 20%
- Other: 2%
- White: 36%
- African-American: 42%

CDC. Available at: www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm

Rising rates of AIDS cases in women in U.S. – 46% HIV cases worldwide

- Proportion of all AIDS cases in women has more than tripled in 15 years, from 7% in 1985 to 29% today
- Leading cause of death in black women ages 25-34 (3rd in black women ages 35-44; 5th overall in women 35-44)

**CDC guidelines (routine, not risk-based) 9/21/06 may benefit women**

- HIV screening in all health-care settings ages 13-64 after patient notified (opt-out screening – assent inferred unless patient declines).1
- HIV testing for those at high risk for HIV infection at least yearly
- General consent for medical care implied; separate written consent not required
- Prevention counseling requirement relaxed
- (Some controversy, state-by-state)2

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**Screening in pregnant women**

- HIV screening should be included in the routine prenatal panel for all pregnant women
- Opt-out screening after the patient is notified about testing
- Repeat screening in the 3rd trimester in areas of elevated rates of HIV in pregnant women or high-risk patient
- Rapid testing during labor if no HIV test documented

---

AB682 signed by Gov. Schwarzenegger in CA 10/12/07

- AB 682 (California HIV Routine Screening bill)
  - Repeals written consent for HIV testing
  - Part of unwritten consent for routine medical care


Case#2

HPI: 39 year old AA female with HIV contracted in '97 2o heterosexual sex, never on HAART (except during pregnancy), presents to clinic 6 months ago after sporadic f/u for past 8 years. Current CD4 count 260 and viral load 80,000.

Pt single mother of two children and has been reluctant to start ARVs (although took during pregnancy). Finally comes to clinic stating “I am willing to try your drugs, but they better not give me side effects”
Case

- PMH remarkable for chronic hypertension with mild renal insufficiency, anemia and grade I peripheral neuropathy
- **Meds:** HCTZ, iron supplements, gabapentin
- **Allergies:** NKDA
- **Social history:** Smokes ½-1 PPD; drinks 2-3 glasses of beer per night; sporadic MJ and crack use; h/o heroin use in past; works in convenience store sporadically; 2 children at home

Case

- **PE:** BP 145/92; Anxious thin AA woman, NAD; OP clear; old track marks, but no current skin abnormalities; S4 present, otherwise exam unremarkable
- **LABS:**
  - WBC 3.9; Hct 32.6; Plt 150; BUN 15; Crea 1.4
  - Baseline HIV phenotype -full sensitivity to all agents except ddl (fold-change 1.94).
- **Question:** What NRTI backbone would you consider for this patient with renal insufficiency, anemia and neuropathy, hoping for no side effects?
ARS question: What NRTI backbone would you choose?

1. Tenofovir + Didanosine
2. Tenofovir + Emtricitabine (Truvada®)
3. Zidovudine + Lamivudine (Combivir®)
4. Abacavir + Lamivudine (Epzicom®)
5. Stavudine + Lamivudine

NRTIs in women

- Mono or dual therapy era, had sex differences in NRTI toxicities (pancreatitis, lactic acidosis, neuropathy)\(^1\)\(^-\)\(^^5\)
- Women still at higher risk for anemia with AZT than men\(^6\)
- TFV-associated renal insufficiency (EAP) higher with lower body weights, lower CD4, older age\(^7\)
- At higher risk for neuropathy than men

I chose ABC/3TC – As safe in women?

- Risk factors for HSR
  - Retrospective analysis of 8038 ABC-treated subjects¹
  - Female sex ↑ odds (OR 1.42) for developing ABC HSR

> ![Risk Factors Diagram]


**HLA*B5701 prevalence worldwide**¹

Now know about HLA*B5701 association with ABC HSR (PREDICT-1², SHAPE), so should test our patient prior to starting ABC³

Case (continued)

- Pt HLA*B5701 negative, so started ABC/3TC/ATZ/RTV
- No ABC HSR
- Had GI side effects on ATZ/RTV and didn’t like food restriction, so switched to Fosamprenavir/RTV (100mg daily\(^1,2\))
- Still GI side effects on RTV

\(^1\)Ruane et al. Plasma amprenavir pharmacokinetics and tolerability following administration of 1,400 milligrams of fosamprenavir once daily in combination with either 100 or 200 milligrams of ritonavir in healthy volunteers. Antimicrob Agents Chemother FebS 2007; 2

Case (cont.)

- Pt very frustrated and asks

All my girlfriends have more side effects on these medications than my men friends – Do women with HIV get more sick from these meds you give out???
What will you tell her about sex differences in adverse events on ARVs?

1. Yes, sex differences in adverse effects exist
2. No, this is all in your head

Sex differences in adverse effects of ARVs

- NRTI toxicity differences well-known and reviewed\(^1\)-\(^7\)
- Sex differences in HAART era frequent\(^8\),\(^9\) and have clinical consequences
  - 1\(^{st}\) HAART discontinuation rates 2\(^{o}\) to toxicities
    > 2x as common in women than men (IcoNa)\(^{10\text{-}12}\)

---

**NVP-induced rashes more common in women**

- More common (15.8% vs 8.4%; RR 4-6)\(^1\-^4\)
- More severe (RR 7.3); 2% rate
- ↑ risk at higher CD4 (trend)
- Same or ↓ rash in pregnancy (5-8%)\(^5\-^8\)


**NVP related hepatotoxicity more common in women**

- **Safety data of NVP\(^1\):**
  - **Women:** 12x ↑ sx hepatotoxicity with CD4 >250 vs. <= 250
  - **Men:** 5x ↑ risk CD4 >400 vs. <= 400
- **S. African trial with NVP\(^2\):**
  - Women 20% grade 3,4 toxicity (12.8% men)
  - 50% hepatotoxicity in women BMI <18.5

\(^1\)“Dear Health Care Professional Letter”, Boehringer-Ingelheim, 2004; \(^2\)Sanne. JID 2005
**Risk factors for NVP-related hepatic toxicity in women**

- Toxicity with systemic sx (rash) 3.2x as common in women
- Pregnancy (19% vs. 4.2%)\(^2-4\)
- Low BMI\(^5\)
- Common to sexes: AST/ALT ↑, HBV, HCV\(^6\), especially genotype 3 (HR 1.9)\(^7\) (treatment of HCV protective\(^8\)), prior toxicity


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**Sex differences in CVD events (M>F) most likely not HAART-related**

- Triglyceride (TG) and LDL increases, HDL decreases relatively more in men than women on HAART (pre-menopausal)\(^1-4\)
- ↑ MI rate in men versus women in DAD, median age 39 (RR 1.99)\(^5-7\)
  - Sex-difference not related to differences in HAART usage
  - Most likely secondary to baseline CVD risk factors
- ↑ in high-risk CVD in males vs females (17 vs 12%) in WIHS/MACS\(^9\)
  - Driven by non-HAART factors (smoking, BP, age, overweight, low income)

Need more comparison data with post-menopausal women

General pattern of fat changes differ by sex

- ↑ central adiposity in women
- Equal rates of peripheral lipoatrophy in both sexes
- ddI\textsuperscript{1,9}, IDV\textsuperscript{2} and d4T\textsuperscript{2,11}
- Patient-described: “Beach ball on sticks”

Summary of adverse events more common in women on HAART

- NVP rashes and hepatotoxicity
- More GI intolerance to older PI regimens\textsuperscript{1-4}, not newer\textsuperscript{5-6}
- Lipid changes less than men, but unclear effect on CVD outcomes
- Women more central adiposity (some role of HAART: d4t→LA; IDV→central fat; ddI→fat loss)
- Ecologic increases in preterm, pre-eclampsia and fetal death with HAART in pregnancy
- Osteopenia HIV-related AND HAART-associated (PIs\textsuperscript{7-11}) so watch in women
**Why do women have more adverse effects? – Probably PK**

**Pharmacokinetics**

- **Bioavailability**
  - Women ↓ acid, slower gastric emptying time (OCPs, pregnancy)
  - Diet differences
  - No consistent differences in gut CYP or p-gp

- **Distribution**
  - Women weigh less
  - More proportional fat
  - Varying plasma volumes
  - Less organ flow
  - Estrogen has effects on plasma binding proteins

- **Metabolism**
  - In vitro: F>M trend
  - Progesterone ↑ CYP2A4 activity
  - Hepatic g-gp M>F

- **Elimination**
  - Smaller organs
  - HepC and liver status

Administration of concomitant medications can affect each stage & vary by sex


**Sex differences in ARV pharmacokinetics**

- Most studies generally show higher plasma concentrations or AUCs of ARVs in women\(^1\): IDV\(^2,3\), LPV\(^4\), SQV\(^5,6\), NVP\(^7,9\), EFV\(^10,11\)

- But few powered to look at association between levels and toxicities or outcomes by sex (WIHS performing\(^12\))

Case (continued)

- Given GI side effects with PIs, consider NNRTIs
- Concerned about NVP given CD4 >250
- Pt gingerly started on efavirenz 600mg po qhs with her ABC/3TC tablet (pt counseled on pregnancy)
- Pt starts having horrible nightmares and insomnia (as well as fantasies of switching providers), but has an amazing immunologic and virologic response
- Question: Any specific reason to think our patient would have more side effects on efavirenz?

ARS: What pharmacogenomic trait may lead to an increase in EFV exposure in our patient?

1. HLA*B5701 rates lower in patients of African descent
2. Cytochrome p450 3A4 (CYP3A4) activity higher in patients of African descent
3. CYP2C19 activity lower in African-Americans than Caucasians
4. CYP2B6 activity lower in African-Americans than Caucasians
Genetic effects on EFV

- CYP450-2B6 is responsible for $\beta$-hydroxylation of EFV and 90% of its clearance
- G$\rightarrow$T change at codon 516 reduces CYP2B6 activity\(^1\)
- Homozygous TT genotype with highest EFV levels
- MDR1 (p-gp) may also affect EFV levels\(^2\)


CNS symptoms on EFV and CYP2B6 variation

- ACTG study in 89 (57%) European-Americans; 50 (32%) African-Americans; and 15 (10%) Hispanics\(^1\)
- CYP2B6 TT genotype more common in AA (20%) than EA (3%) and associated with higher EFV AUC (p 0.0001)

\(^1\)Haas et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS. 2004
CNS symptoms on EFV and CYP2B6 variation

- CNS symptoms in the CYP2B6 TT patients were higher at week 1 of therapy (p = 0.036)\(^1\)

- But no relationship between CYP2B6 TT and virologic response/resistance\(^2\)

1 Haas et al. Pharmacogenetics of efavirenz and central nervous system side effects. AIDS. 2004; 2 Haas et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir. JID 2005

Trial of reducing EFV dose in TT patients

- Looked at CYP2B6 516 genotype of 111 Japanese patients and saw same trend

1 Gatanaga et al. Successful efavirenz dose reduction in HIV Type1-infected individuals with cytochrome p450 2B6 *6 and *26. CID November 1, 2007
Reducing EFV dose for CYP2B6 TTs

- Reduced dose to 400mg or 200mg of 12 of those treated TT patients (also started 5 naives on 400mg)
  - All remained undetectable and levels >minimum target [ ].
  - All reported improvement in CNS symptoms

**Graph**

Case (continued)

- You send 10 strands of pt’s hair to Gandhi project and find that EFV levels exceed those of 90% in her study¹ (CYP2B6 516 indeed TT)
- Reduce dose of EFV to 400mg po qhs
- New regimen of Epzicom 1 tab po qhs and EFV 400mg po qhs → good immunologic and virologic response, side effect free

**Question:** Do men and women do equally as well on therapy, besides the side effects?

¹Gandhi et al. Hair levels of antiretrovirals are an independent predictor of virologic success (submitted, December 2007)
ARS: Do men and women have different clinical responses on therapy?

1. Yes, women have better virologic responses than men
2. Yes, women have worse virologic responses than men
3. Yes, women have lower rates of survival than men
4. No, men and women do equally as well on antiretroviral therapy in terms of virologic and clinical responses

Virologic, immunologic responses similar

- Virologic responses
  - Baseline viral loads lower in women, but responses similar$^{1-3}$
- Immunologic responses
  - Higher baseline CD4 counts in women, but parallel increases$^{2-6}$

Progression to new AIDS diagnoses or death same in both sexes if adjusted

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>~2 yrs</td>
<td>Johns Hopkins clinic cohort¹,²</td>
</tr>
<tr>
<td>3 yrs</td>
<td>Swiss HIV Cohort Study²</td>
</tr>
<tr>
<td>4 yrs</td>
<td>London clinic cohort, 1st HAART on³</td>
</tr>
<tr>
<td>5.4 yrs</td>
<td>Italian Antiretroviral Treatment Group, 1st HAART onwards⁴; CASCADE (22 cohorts)⁵</td>
</tr>
<tr>
<td>6-7 yrs</td>
<td>EuroSIDA cohort, 1st HAART on⁶; Spanish hospital network, ’97-'04⁷</td>
</tr>
</tbody>
</table>


Reasons for mortality in HIV patients may differ by sex

- Comparison study of causes of mortality in Multicenter AIDS Cohort Study (MACS) and Women’s Interagency HIV Study (WIHS)¹
- Higher rates accident or injury-related mortality in women vs men (2.96 vs. 0.79/1000)
- Risk factors for death varied by gender

**WOMEN**
- Decreased CD4
- Unemployment
- Higher EtOH use
- IVDU

**MEN**
- Higher education
- Depression
- Higher # of sex partners

¹Hessol N. Mortality among participants in the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study. CID 2007
Disparities usually explained by access: Use of HAART in the USA by Race and Gender

Cunningham WE et al. JAIDS 2000; McNaughten et al. JAIDS 2003; Pence. The Influence of Psychosocial Characteristics and Race/Ethnicity on the Use, Duration, and Success of Antiretroviral Therapy. JAIDS 2007

Community beliefs about HIV

500 African Americans surveyed by phone
(51% high school and 49% some college or more; 53.4% <$35,000 and 46.6% >$35,000 annual income)

- Institutions are trying to stop HIV 75.4 %
- AIDS is a form of genocide 15.2 %
- AIDS was produced in a government lab 26.6 %
- People who take new meds are guinea pigs 43.6 %
- Cure for AIDS exists, but withheld from poor 53.4 %
- Information about AIDS is being withheld 58.8 %

Case (continued)

The patient feels well. Had been counseled on EFV and teratogenicity prior to starting new regimen and stated she had no intention of pregnancy.

However, new boyfriend (HIV-negative) tells pt that he wants to have baby with her and pt agrees.

Special preconception points with serodiscordant couples

- Surveys indicate 25-33% of HIV-positive women desire childbearing\(^1\)\(^3\) (63% in Nigeria\(^4\))
- Preconception labs:
  - Rubella, Varicella immunity screen
  - Toxo IgG
  - Hep A, B, C serology
  - Hb electrophoresis
- Preconception vaccines
  - MMR if CD4 >200
  - Pneumovax, Tdap, Influenza
  - Hepatitis A/B
- Prenatal vitamins (400-800mcg folate)
  - Increase folate to 4-10mg a day if on folate antagonist (TMP-SMZ)
- Counseling
  - Domestic violence, drug/EtOH abuse, supports, milk bank/formula

Insemination options

- HIV+ ♀ with HIV- ♂: Assisted insemination (role for PREP/PEP with timed coitus)

- HIV- ♀ with HIV+ ♂:
  - Wash sperm (spermatozoa lack CD4/CCR5/CXCR4, so HIV RNA in non-sperm cells/fluid) x 2 after gradient centrifugation (>99.99% HIV free)
  - Controversy about testing for HIV PCR after washing (no seroconversions)
  - IUI, IVF or intracytoplasmic sperm injection
  - CA Senate law bill allows sperm washing in CA as of 1/08


Mother-to-Child Transmission in the US Over Time

<table>
<thead>
<tr>
<th>Year</th>
<th>Transmission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993: WITS</td>
<td>24.5%</td>
</tr>
<tr>
<td>1994: PACTG 076</td>
<td>7.6%</td>
</tr>
<tr>
<td>1997: PACTG 185</td>
<td>5.0%</td>
</tr>
<tr>
<td>1999: WITS</td>
<td>3.3%</td>
</tr>
<tr>
<td>2001: PACTG 247</td>
<td>2.0%</td>
</tr>
<tr>
<td>2002: PACTG 316</td>
<td>1.5%</td>
</tr>
<tr>
<td>2005</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Decline due to:
- More HIV testing in prenatal visits
- Increase in use of HAART by HIV+ women
- Increase in elective C-section by HIV+ women
ARS: Can this patient remain on her same regimen? She is happy on it

1. No, the efavirenz should be switched to nelfinavir
2. No, the abacavir should be switched to zidovudine
3. Yes, we finally found a regimen that works!
4. No, the efavirenz should be switched to a non-nelfinavir PI

Which ARVs NOT to use in pregnancy

- Efavirenz - teratogen
  - Retrospective Antiretroviral Pregnancy Registry reports
  - 4 Cases human infants with significant CNS defects with 1st trimester exposure to EFV (meningomyelocoele, Dandy-Walker)
- ddI/d4T combination (lactic acidosis, hepatic)
- NVP if CD4 >250
- Nelfinavir with EMS (ethylmethyl sulfonate) contamination²

### ARVs and Pregnancy – Start 2\(^{nd}\) trimester

<table>
<thead>
<tr>
<th>ARVs and Pregnancy</th>
<th>NRTI/ NtRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>FI/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td>AZT 3TC</td>
<td>NVP(^1)</td>
<td>LPV/r (3(^{rd}) trim: increase dose)*</td>
<td>T-20, Mavariroc, Raltegravir</td>
</tr>
<tr>
<td>Alternate</td>
<td>ddl, FTC, d4T, ABC</td>
<td>IDV RTV SQV(sgc)/r</td>
<td>EFV(^3) DLV(^4)</td>
<td>NFV(^7)</td>
</tr>
<tr>
<td>Not recommended</td>
<td>ddC(^2)</td>
<td>TFV</td>
<td>FPV, ATV(^6), Darunavir, Tipranavir</td>
<td>T-20, Mavariroc, Raltegravir</td>
</tr>
<tr>
<td>Insufficient data</td>
<td>TFV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Rodent studies show potential for teratogenicity and developmental toxicity.
\(^2\)Rodent data shows potential for teratogenicity and carcinogenicity.
\(^3\)Primate/human studies show teratogenicity.
\(^4\)Rodent data shows potential for teratogenicity and carcinogenecity.
\(^5\)Theoretical concern for hyperbilirubinemia, accumulating data on safety.
\(^6\)Increase dose from 2 tabs po bid to 3 tabs po bid (Maltrex) in 3\(^{rd}\) trimester.
\(^7\)EMS as preservative.

---

**ARS: You switch patient to ABC/3TC/Kaletra. Can she stay on same dose throughout pregnancy?**

1. No, the abacavir should be increased during the 3\(^{rd}\) trimester
2. No, the Kaletra dose should be decreased during the 3\(^{rd}\) trimester
3. Yes
4. No, Kaletra dose should be increased during the 3\(^{rd}\) trimester

*Available at [http://AIDSinfo.nih.gov](http://AIDSinfo.nih.gov).*

November 2007 DHHS Guidelines.
Remember dosing changes

- Kaletra – Increase to 3 tabs po bid during 3rd trimester (from 2 tabs bid) due to PK changes\(^1\)
- Atazanavir – No PK differences during 3rd trimester\(^2\), so no dose adjustment

\(^1\)Stek AIDS 2006; \(^2\)Ripamonti. AIDS 2007

Current USPHS Guidelines for Prevention of Mother-to-child Transmission

- **Mother’s plasma HIV-1 RNA >1,000 copies/mL**
  - Combination highly active antiretroviral therapy (HAART)
  - Elective C-section if HIV-1 RNA >1,000 copies/mL near delivery
- **Maternal plasma HIV-1 RNA <1,000 copies/mL**
  - HAART or use of AZT alone
- **No treatment prior to labor**
  - During birth and after birth (for baby) of regimens of AZT, AZT/3TC, nevirapine, or AZT/nevirapine, single dose of Truvada® may decrease NVP resistance\(^2\)
- **No treatment prior to or during labor**
  - Infant prophylaxis for 6 weeks with AZT after birth
  - Some clinicians use combination therapy (HAART)

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Make your promise now at www.unsrtlaidscampaign.org

HIV/AIDS is a viral disease that affects the body's immune system. It is spread through sexual contact, intravenous drug use, and blood-to-blood contact. The symptoms of HIV/AIDS can vary, but they can include fever, fatigue, and weight loss.

By making a promise to stop AIDS, you are taking a step towards preventing the spread of this disease. Your actions can make a difference in the lives of others.

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