

The Essentials of Providing HIV Primary Care

All Grantees Meeting
Wardman Park Marriott
August 28, 2008

*Michael Wong, MD
Assistant Professor of Medicine
Harvard Medical School
Division of Infectious Diseases
Beth Israel Deaconess Medical Center*

OBJECTIVES

- HIV - Overview
- Testing
- Stages of Infection and Clinical Manifestations
- Evaluation and Work Up: It's the Whole Patient
- Antiretroviral Therapies
- Standards of Care

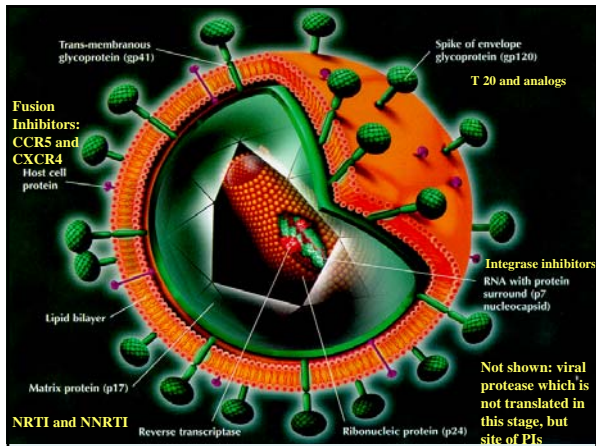
HIV

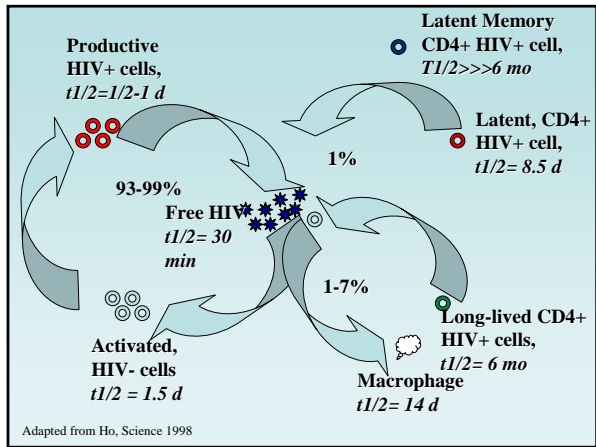
HIV: the Human Immunodeficiency Virus

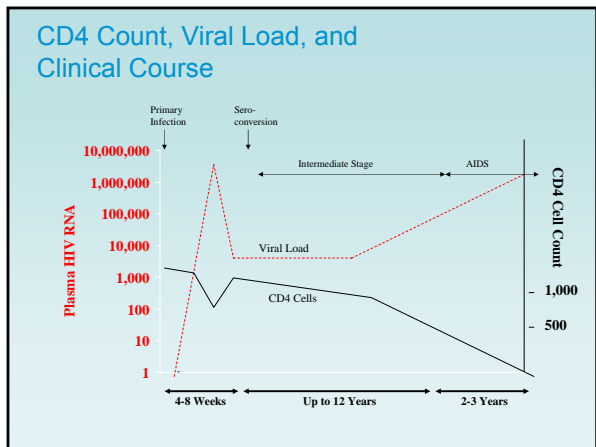
AIDS: Acquired Immunodeficiency Syndrome (defined by either opportunistic infections, malignancies, or CD4 count less than 200cells/mL)

Retrovirus: an RNA virus that requires a virally encoded enzyme, Reverse Transcriptase (RT) to create a double-stranded nucleic acid sequence that can insert into a DNA strand

CD4: Refers to a surface protein on specific T lymphocytes. This is the primary target receptor for HIV.

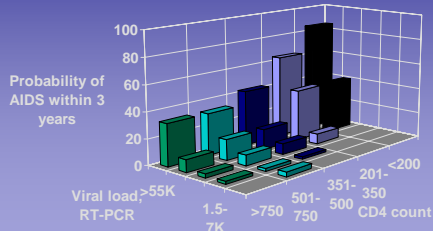






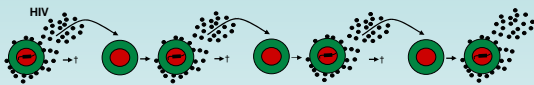
Risk of AIDS by CD4 and VL

Probability of developing AIDS by CD4 count and HIV viral load



Adapted from Mellors, J, et al, Ann Int Med, 1997;126:946-54

Sources of Plasma Virus



- ⑩ Cells infected/day = $\delta T^* = cV/2N \sim 3V$
- ⑩ A new mutation arises in every third newly infected cell
- ⑩ Therefore, mutations/day $\sim V$
- ⑩ Genome is 10 kb; thus, 30,000 mutations are possible
- ⑩ At $V = 30,000$ copies/mL, every possible mutation arises once a day somewhere in the body!

Adherence and HIV

- ⑩ Adherence correlates with viral suppression and clinical outcome

Level of adherence	% with undetectable viral load
>95%	81%
90-95%	64%
80-90%	50%
<80%	6%

90-95% 64%

80-90% 50%

- Ⓢ Taking between 60 and 90% is associated with increased risk development of resistance
- Ⓢ Decreased adherence is associated with increased morbidity and mortality
- ⑩ In a b.i.d. regimen, less than 1 dose/week can be missed

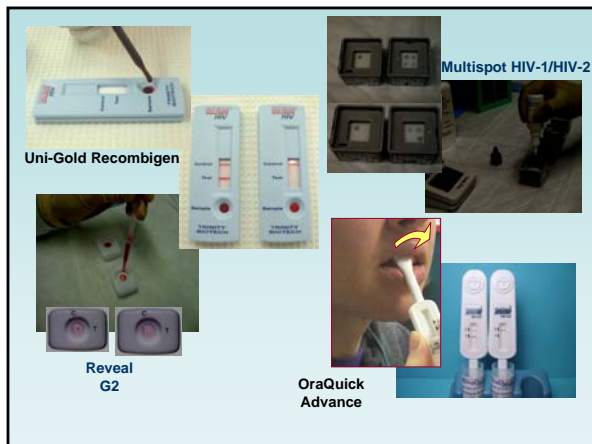
HIV Testing

Diagnostic Testing: HIV Antibody

The gold standard for diagnosis of HIV infection when used with confirmatory Western Blot

Antibody conversion typically 22-27 days following infection¹

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



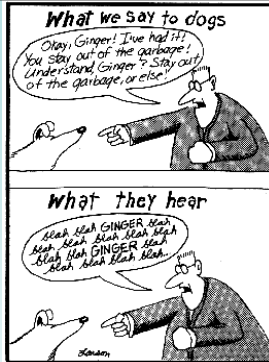
Confirmatory Testing- Positive Rapid test

- ⑩ Confirmatory test is essential (not just another EIA)
 - ⑩ Western blot (presently)
- ⑩ Follow-up testing of persons with negative or indeterminate Western blot results after 4 weeks

Rapid Testing: False Positives

1. False Positive rates high
 1. Pre-market data suggested sensitivity to be 99.8%
 2. Post-market results indicate sensitivity to be 99.1%
 1. NY, 35 false positive results reported out of 3754 known negative clients tested.
 2. SF, 7800 tests performed; 222 positive; 47 false positive, 175 confirmed positive.
2. False Negative results less common
3. PCPs need to learn how to explain the discrepancies (this is hard for any of us)

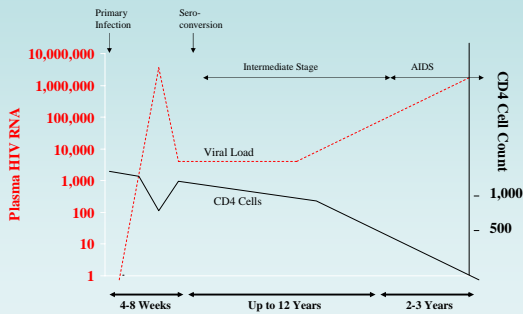
What we say to patients: "The OraSure is positive, but there are false-positive cases so you may be HIV negative. This doesn't mean you have HIV. We need to retest with a standard blood test."



What patients hear us say: "The Orasure is positive"
(OHIMGOD!!!!!!!, I'm positive),
"blah, blah, HIV, blah"
(What is happening?)
"blah, blah, retest, blah."

Stages of Infection

CD4 Count, Viral Load, and Clinical Course



Acute HIV Infection

Signs and symptoms typically begin 1-4 weeks post-exposure

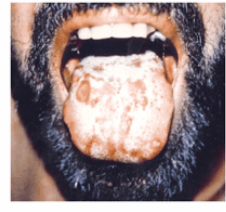
Associated Signs and Symptoms (Frequency)

- Fever (96%)
- Lymphadenopathy (74%)
- Pharyngitis (70%)
- Rash (70%)
 - Erythematous maculopapular with non-pruritic lesions on face and trunk & sometimes extremities, including palms & soles
 - Mucocutaneous ulceration of mouth, esophagus, or genitals
 - This may look just like acute EBV or CMV associated mononucleosis!



Acute HIV Infection

- Myalgia or arthralgia (54%)
- Diarrhea (32%)
- Headache (32%)
- Nausea and Vomiting (27%)
- Hepatosplenomegaly (14%)
- Weight loss (13%)
- Thrush (12%)



Acute HIV Infection

- Neurologic Symptoms (12%)
 - Meningoencephalitis or aseptic meningitis
 - Peripheral neuropathy or radiculopathy
 - Facial palsy
 - Guillain-Barre' syndrome
 - Brachial neuritis
 - Cognitive impairment or psychosis

Stages of HIV Infection

Stage 4 – AIDS

- AIDS diagnosis confirmed if a person with HIV develops one or more of a specific number of severe opportunistic infections or cancers
- CD4 <200 or percentage < 14 %
- AIDS diagnosis NEVER goes away even when the patients condition improves and no longer meets the criteria*

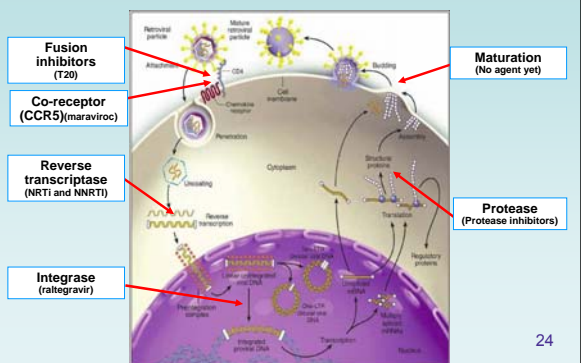
When do the the OIs occur?



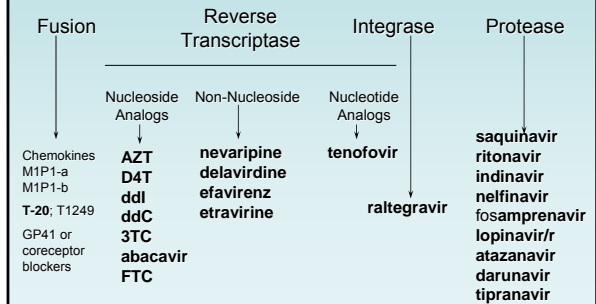
At any time though more common when CD4 count is low:
Malignancies, MTB, *M kansasii*
CD4 >200:
recurrent CAP, recurrent *Salmonella*
CD4 <200, >100:
PJP
CD4 <100, >50:
MAI
CD4 <50:
CMV, JCV, Cryptococcal meningitis,
Cryptosporidiosis/Isospora,
Toxoplasmosis

HIV Life Cycle and Targets of ARV therapy

Retrovirus life cycle



Anti-Retrovirals

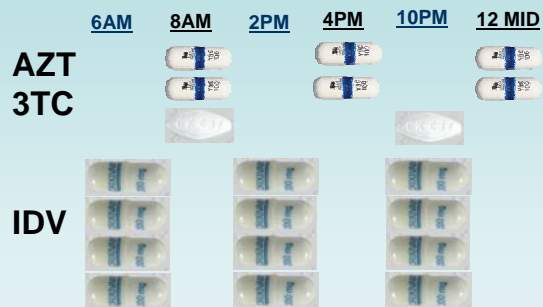


Treatment

Primary care focus-

- Monitor disease-CD4 count/viral load
- Appropriate medications and assess adherence
- Manage comorbid states
- Prevention
 - Progression of disease
 - Opportunistic infections
 - Other comorbid states
 - Spread to others- Secondary Prevention
- **Remember- YOU ARE NEVER ALONE IN THIS; ALWAYS PARTNER WITH AN EXPERIENCED HIV PROVIDER.**

3-Drug Combination ART: 1996



PLUS 1.5 liters of hydration/day

Adapted from Glesby, NY/NJ AETC

3-Drug Combination: 2006

TDF/FTC/EFV



Adapted From Glesby, NY/NJ AETC

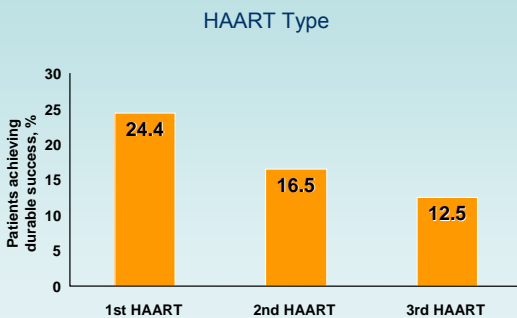


Assess Adherence

⑩ Virologic suppression success is based upon:

- >95% adherence
- Baseline HIV resistance mutations
- Patient tolerance of the ARV and side effects
- Adverse drug-drug interactions (e.g., don't use D4T and ZDV together; increase PI dosing if used with PPI or EFV; beware effects of RIPE and ARVs)
- Lack of Drug Interruptions-
 - Intended-- the old structured treatment interruptions (NO!)
 - Unintended--by pt or pharmacy or renewed prescriptions or ADAP paperwork

Durable Response: Results

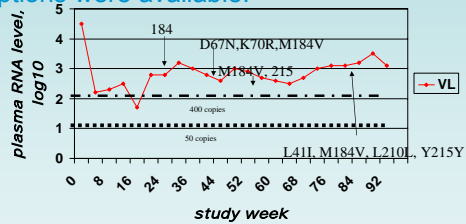


Palella F.J., et al. *N Engl J Med*, 1998; 338: 853-60

Conventional wisdom is that adherence must be 95% to reduce risk of mutation
This means:

- ⑩ If you are on a bid regimen and you miss 1 dose out of 14 your adherence is 93%
- ⑩ If you are on a bid regimen and you miss 2 doses out of 14, your adherence is 86%
- ⑩ If you are on a qd regimen and you miss 1 dose out of 7 your adherence is 86%

Stepwise appearance of mutations in subjects with ABC virologic failure- the provider accepted a failing regimen when options were available.



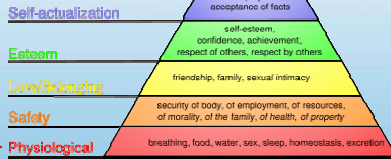
Melby, T, et al. 8th CROI, Chicago, 2001, #448

Standards of Care

Always work with your patient where they are and remember this is dynamic.



For many patients, HIV therapy is up here, not a basic need.



To Providers, HIV therapy is here

Maslow's Hierarchy of Needs

INITIAL COMPREHENSIVE EXAM: HISTORY

- **HPI, PMH, ROS, FSH**
 - Detailed OB/GYN hx including PAP results for women
 - Comorbidities
 - Psychosocial evaluation including mental health and substance abuse hx
 - Hx of TB testing, exposure and/or prophylaxis
 - Present medications, allergies
 - Immunization Record
- **Involve Social Work/Case Management-**
 - Financial Screening; ADAP application; Housing assessment; Insurance or payor coverage and paperwork

INITIAL COMPREHENSIVE EXAM: PHYSICAL EXAMINATION

- Comprehensive physical examination
- Including oral examination
 - Pelvic examination for women
 - Anal examination for men and women

**INITIAL COMPREHENSIVE EXAM:
BASELINE CLINICAL DATA**

- CBC with diff
- G6PD
- Chem 7, LFTs, LDH
- Fasting blood sugar
- Fasting lipids
- Urinalysis with PRO:CR
- PAP smear*
- Anal PAP*
- *if PAP positive even for LSIL, get HPV typing
- **Some also advocate BHCG for women of childbearing potential
- STD screening:
 - RPR
 - GC & Chlamydia
- Exposure screening:
 - Toxoplasma IgG
 - CMV IgG
 - Hepatitis A, B, C serologies
 - PPD
- HIV specific Testing:
 - CD4 T-cell count and %
 - HIV RNA VL
 - Genotypic resistance test
 - Tropism assay if considerin CCR5 antagonist
 - HLA-B*5701 testing
- CXR

COUNSELING

- **Treatment Adherence**
 - Assessment for readiness for tx
 - Risks, benefits, challenges of tx
 - Drug side effects -assessment and tx
- **Pregnancy Prevention/Achievement**
- **Advanced Directives**
- **HIV Prevention**

**When to start:
DHHS Guidelines**

Treatment should be initiated

- History of AIDS
- CD4 <200 cells/ml
- CD4 200-350 cells/ml
- Pregnant women
- HIV ITP, HIV Encephalitis/encephalopathy
- Patient with HIV- associated nephropathy
- Patient with Hepatitis B if Hep B tx is indicated

Optimal time in asymptomatic patients CD4 >350 cells/ml is not well defined

- Patient scenarios and co-morbidities should be considered
- Patient acceptance of ARVs (even Atripla)- start the adherence counseling EARLY

Why start at CD4 ≤ 350 cell/mm³?

The cut off to start is arbitrary

The earlier one starts, the better one does for \leq CD4 500

Balancing toxicity, adherence, and survival

As drugs get less toxic and easier to take, balance changes

NB: ***Patients must be ready to take medications BEFORE you prescribe them***

The viral load is the speed of the train; we want to

STOP THIS TRAIN.



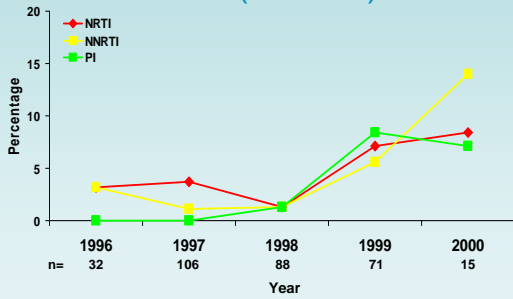
When to Use Resistance Testing

	IAS-USA ^[1]	DHHS ^[2]	European ^[3]
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis	—	—	Recommend
Chronic, Rx naive	Consider*	Recommend	Strongly consider*
Failure	Recommend	Recommend	Recommend
Pregnancy	Recommend	—	Recommend*
Pediatric	—	—	Recommend [†]

*Especially if exposure to someone receiving antiretroviral drugs is likely or if prevalence of drug resistance in untreated patients $\geq 5\%$ (European: $\geq 10\%$).

1. Hirsch MS, et al. Clin Infect Dis. 2003;37:113-128.
2. Available at: www.cdc.gov.
3. Vandamme AM, et al. Antivir Ther. 2004;9:829-848.

Primary Infection with Drug Resistant HIV (>10 fold)



Little SJ, et al., 8th CROI, Chicago, 2001. #756; NEJM 347:385 2002

Primary Infection Resistance: Clinical Implications

⑩ Commonly transmitted mutants:

- RT: 184; 215; 69S
- RT (NNRTI): 103; 181
- Protease: 82; 84; 90

⑩ Delayed to time of viral suppression (p=0.05)

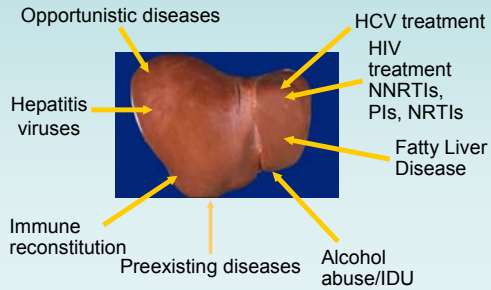
⑩ Shorter time to first viral failure (p=0.05)

Little SJ, et al., 8th CROI, Chicago, 2001. #756; NEJM 347:385 2002

What to Start: DHHS Guidelines 1/2008 (1 from A and 1 from B)

	Column A		Column B
	NNRTI	PI	2-NRTI
Preferred <small>(alphabetical QD; BID)</small>	EFV	ATV/RTV FPV/RTV LPV/RTV	ABC/3TC TDF/FTC
Alternative <small>(alphabetical QD; BID)</small>	NVP	ATV FPV/RTV LPV/RTV FPV SQV/RTV	AZT/3TC DDI/3TC

Liver in HIV-Infected Patients



Courtesy of Mark Sulkowski.

HEPATITIS

HIV-HCV co-infection rates are 30-90% in US
HIV-HBV co-infection rates are 10-30% in US
For every person infected with HIV there are 4-5 infected with Hep C
NASH-non alcoholic steatotic hepatitis- e.g. fatty liver disease- common in poorly controlled DM, families; medications make this worse including ARVs.

Risk-benefit analysis of coronary heart disease and HAART

Average calculated increase in CHD events = 0.14% per year

Mortality rates in HIV-infected patients fell by 50% in the USA

CHD = coronary heart disease

Adapted from Grunfeld C, et al. 6th CROI, Chicago, 1999; Palella FJ, et al. *N Engl J Med*, 1998; 338: 853-60

Mental Health

Depression

5-10% of general population; 60% of HIV+ population

Some ARVs will make worse

Can be mistaken for signs of advancing HIV

HUGE self medication with ETOH or other agents

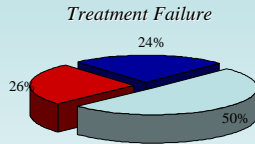
Bipolar disorder, schizophrenia also disproportionately high in HIV+ population- significant self medication

MONITORING VISITS EVERY 3 MONTHS

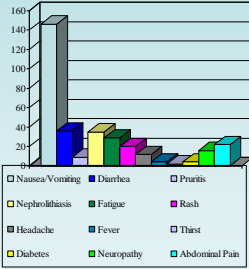
- HPI
- Risk Behavior Assessment
- Medication Assessment and Adherence
- CD-4 and Viral load monitor
- Safety Labs- ARV based
- Preventive care and screening for non-HIV related conditions
- Mental Health Assessment
- Nutritional Assessment
- Counseling



Request for Change, by Treatment Failure and Drug Intolerance



- High Viral Load
- Low CD4 Ct
- No Response

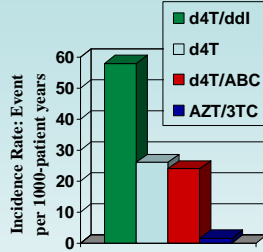


Drug Intolerance

Wong MT, et al, All Titles Conference, 1998

Lactic Acidosis

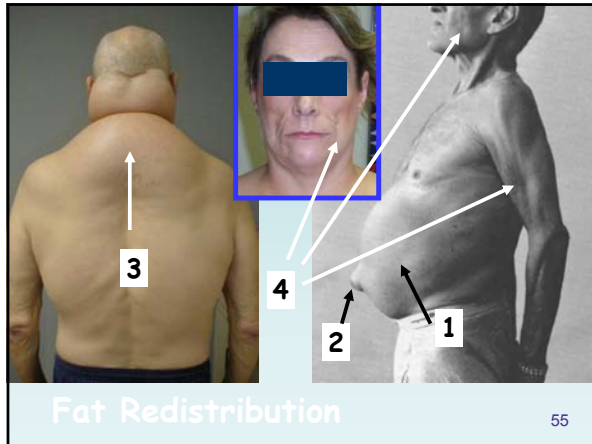
NRTI containing regimen with lacticacidemia and either: 1) GI complaints or 2) unexplained elevation in ALT
 Incidence 14.5/1000 persons-years
 50% presented with ALT elevation; 50% with GI complaints
 Median time to normalization was 50 days.



Loneragan et al, 8th CROI, Chicago, 2001; #624

LIPODYSTROPHY

Body fat redistribution
 Fat accumulation (PIs, NNRTIs to lesser extent)
 Loss of fat in face and extremities (ddI, d4T, ABC)
 Hyperlipidemia (PIs >> NNRTI/NRTI/II); associated with 2-4 times CAD rates
 Noted in HIV+ people who have never taken ART



ANNUAL REQUIREMENTS

- Comprehensive Physical Examination
- Basic clinical data
- PAP for women q. 12 months
- Anal PAP
- Update immunizations (HAV, HBV, Tdap, Pneumovax)
- PPD
- Mental Health Assessment
- Substance Abuse Assessment
- Dental Health Assessment
- Ophthalmologic Assessment (if CD4 below 200)

Summary

- ⑩ We have many advances in HIV care
- ⑩ HIV Treatment is much more comprehensive than “just some medications”
- ⑩ Adherence to ARVs is key to success

10 Always,
always,
always partner
with an
experienced
HIV Provider

10 Always,
always,
always work
with your
patient



For many patients, HIV therapy is up here, not a basic need.

