Perinatal Care and Prevention

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Objectives

- Develop patient centered, team based, treatment and delivery plans to prevent perinatal HIV Transmission
- Describe antiretroviral treatment for people living with HIV infection who are pregnant
- Provide perinatal HIV prophylaxis to exposed infants based on current DHHS guidelines

Poll (free text)

What patient care groups are represented in the audience?

Case

- BP is a 23 year old woman diagnosed with HIV at age 16 following a rape. Multiple complications.
- Nonadherence to antiretrovirals and outpatient appointments for last 2 years
- Spontaneous abortion after sepsis in 2016
- Entered into perinatal care at 18 weeks gestation in June of 2017
- Missed HIV clinic appointments during pregnancy – ID clinic not aware of pregnancy until last trimester
- Delivered baby with HIV infection

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HIV Transmission from Mother to Baby

An **HIV+ pregnant woman** can transmit HIV to her baby **3 WAYS**:

+ During pregnancy
+ During vaginal childbirth
+ Through breastfeeding

- 25% risk of perinatal transmission in absence of therapy
  - 20% before 36 weeks
  - 50% between 36 weeks and delivery
  - 30% active labor and delivery
- Less than 1% risk if
  - Suppressive antiretroviral therapy (ART) during pregnancy
  - Postnatal infant antiretroviral prophylaxis
  - C-section & AZT if indicated
  - Avoidance of breastfeeding

Connor EM et al. N Engl J Med.1994;331:1173-80.
Kourtis AT et al. JAMA. 2001;285;709-12.

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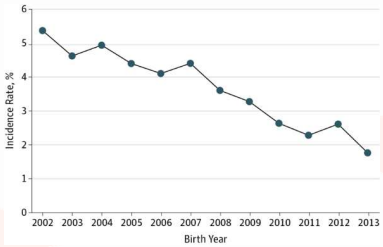
Estimated Incidence Rates of Perinatal HIV in U.S. 2002-2013



Taylor AW et al. Estimated Perinatal HIV Infection Among Infants born in the United States, 2002-2013. JAMA Peds 3/20/17.

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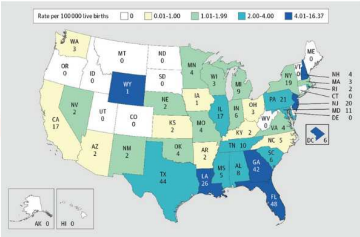
Estimated Numbers and Rates of Perinatally Acquired HIV in Children, U.S. 2010-13



Taylor AW et al. Estimated Perinatal HIV Infection Among Infants born in the United States, 2002-2013. JAMA Peds 3/20/17.

Poll

When should pregnant women be screened for HIV?

A) At entry into care for pregnancy

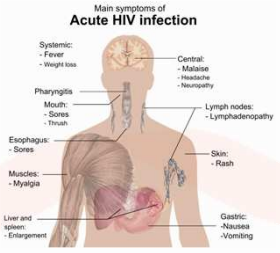
B) If they have any signs or symptoms suggestive of acute HIV

C) In the 3rd trimester if at risk of HIV acquisition

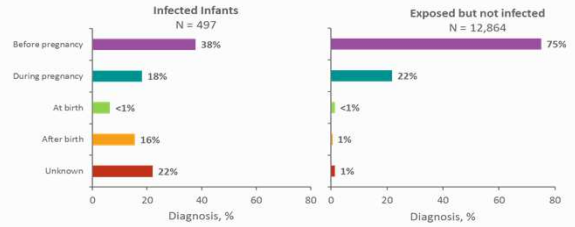
D) All of the above

Screening for HIV

- At presentation for pregnancy care
- Repeat in 3rd trimester if at risk of HIV acquisition
- Signs or symptoms of acute HIV if pregnant or breastfeeding
  - Check HIV viral load as well as 4th generation Ag/Ab test



Time of Maternal HIV Testing among Children with Diagnosed Perinatally Acquired HIV Infection and Children Exposed to HIV, Birth Years 2009–2013—United States and Puerto Rico



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.

CDC. Pediatric HIV Surveillance (through 2016) available at https://www.cdc.gov/hiv/library/slidesets/index.html. Accessed 2.26.18.

Pregnancy Status and Risk of HIV Acquisition

Relative risk of HIV acquisition

Reproductive Stage	Base Model* RR (95% CI)	p-value	Adjusted Model** RR (95% CI)	p-value
Non-pregnant / postpartum	1.00	--	1.00	--
Early pregnancy through postpartum	4.97 (2.95, 8.38)	<0.001	2.76 (1.58, 4.81)	<0.001
Early pregnancy	3.20 (1.24, 8.25)	0.02	2.07 (0.78, 5.49)	0.14
Late pregnancy	5.54 (2.62, 11.69)	<0.001	2.82 (1.29, 6.15)	0.01
Postpartum	7.80 (3.04, 20.02)	<0.001	3.97 (1.50, 10.51)	0.01

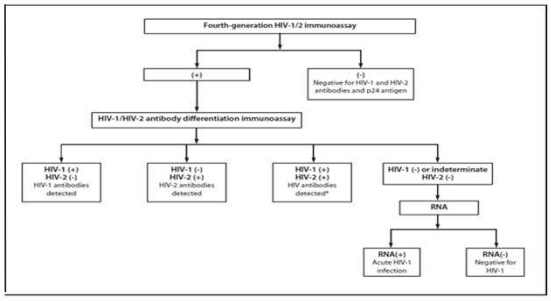
*Adjusted for condom use, reproductive stage
**Adjusted for condom use, reproductive stage female age, active PrEP use, HIV RNA of male partner

Thomson K et al. CROI 2018. Abstract 45.

Case

- Priscilla is a 32 year old woman who presents in her 4th pregnancy with rupture of membranes at 24 weeks and 3 days gestation
- No prenatal care
- She tested positive for gonorrhea, but negative for chlamydia and syphilis
- Her 4th generation HIV test had an indeterminant result
  - Ag/Ab test positive
  - Ab differentiation was negative
  - HIV viral load pending – run only once a week

HIV Testing Algorithm



https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6224a2.htm

Case

- Vaginal delivery 6 days after presented to hospital
- Baby fed formula and mother's breast milk stored until HIV viral load resulted
- Viral load 14 million copies/mL
  - Resulted 12 days after test drawn
- Baby tested HIV positive

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AIDSinfo

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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www.aidsinfo.nih.gov/guidelines

Preconception Counseling

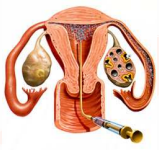
- Safer sex practices (AI)
- Elimination of alcohol, tobacco and other drugs of abuse (AII)
- All HIV infected women should be on antiretroviral therapy (ART) with fully suppressed HIV viral load before conception (AII)

Pre-Conception Considerations

- For concordant and discordant couples
  - Partners should be screened and treated for genital tract infections before attempting conception (AIII)
  - Infected partners should attain maximal virologic suppression before trying to conceive (AIII)

Discordant Couples: Woman With HIV Infection

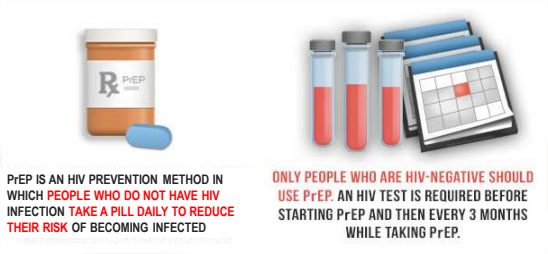
- Assisted insemination at home or in a provider's office with a partner's semen during the peri-ovulatory period **(AIII)**



Discordant Couples: Man With HIV Infection

- Donor sperm from an HIV-uninfected man with artificial insemination is the safest option **(AIII)**
- Semen preparation techniques ("sperm washing") coupled with either intrauterine insemination or *in vitro* fertilization should be considered **(BII)**
- Semen analysis is recommended for HIV-infected men before conception **(AIII)**

Pre-exposure Prophylaxis



PrEP IS AN HIV PREVENTION METHOD IN WHICH PEOPLE WHO DO NOT HAVE HIV INFECTION TAKE A PILL DAILY TO REDUCE THEIR RISK OF BECOMING INFECTED

ONLY PEOPLE WHO ARE HIV-NEGATIVE SHOULD USE PrEP. AN HIV TEST IS REQUIRED BEFORE STARTING PrEP AND THEN EVERY 3 MONTHS WHILE TAKING PrEP.

http://aids.gov/hiv-aids-basics/prevention/reduce-your-risk/pre-exposure-prophylaxis

Care for the HIV-infected pregnant woman

Antiretroviral Therapy in Pregnancy

- Start as soon as possible, even prior to results of genotype
  - Modify therapy later if needed
- French Perinatal Cohort
  - 8075 HIV-infected mother-infant pairs
  - 2000 to 2011
  - Mothers received ART, delivered live-born children with determined HIV status, and did not breastfeed

DHHS Perinatal Guidelines October 26, 2016 available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed 2.1.17.
Mandelbrot L, et al. Clin Infect Dis. 2015 Dec 1;61(11):1715-25.

French Perinatal Cohort

- Overall rate of perinatal transmission 0.7%
- 2651 children born to women on ART prior to conception, ART throughout pregnancy, HIV viral load < 50 copies/mL at delivery
  - No HIV transmission
- Regardless of viral load at birth, risk of transmission varied based on when ART was started
  - ART prior to conception 0.2%
  - ART started in first trimester 0.4%
  - ART started in second trimester 0.9%
  - ART started in third trimester 2.2%

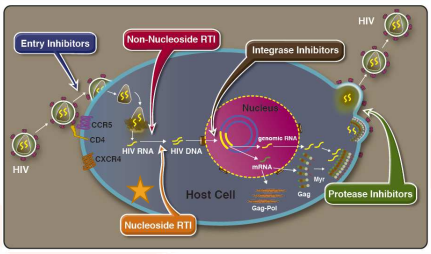
P < .001

Mandelbrot L, et al. Clin Infect Dis. 2015 Dec 1;61(11):1715-25.

Medications in Pregnancy

- Many physical changes occur in pregnancy that affect drug pharmacokinetics
  - Decrease in serum proteins
  - Increased plasma volume
  - Increase in kidney filtration
  - Delayed stomach emptying
- What does this mean for the pregnant woman?
  - May have to take higher doses or take ART more often to get good blood and placental levels

HIV Life Cycle



http://depts.washington.edu/nwaetc/Pill_Chart.pdf

Preferred Regimens in Pregnancy

2 NRTIs + PI/r OR INSTI

NRTI = Nucleoside Reverse Transcriptase Inhibitor
PI/r = Ritonavir boosted protease inhibitor
INSTI = Integrase Strand Transfer Inhibitor

DHHS Perinatal Guidelines October 26, 2016 available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed 2.1.17.

Preferred 2-NRTI Backbone

- **Abacavir/lamivudine (Epzicom®)**
  - HLA-B*5701
  - HIV viral load > 100,000 – don't combine with ATV/r or EFV
- **Tenofovir (TDF)/emtricitabine (Truvada®)**
  - Treats Hepatitis B
  - Potential renal toxicity
- **Tenofovir (TDF)+ lamivudine**
  - Treats Hepatitis B
  - Potential renal toxicity

DHHS Perinatal Guidelines October 26, 2016 available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed 2.1.17.

Preferred Protease Inhibitors

- **Atazanavir/r (Reyataz® + Norvir ®) + preferred 2-NRTI backbone**
  - 300 mg once daily + ritonavir 100 mg daily with food – many would increase atazanavir dose to 400 mg daily in 2nd and 3rd trimesters
  - Maternal hyperbilirubinemia
  - Interactions with acid reducing agents
  - Requires food for absorption
- **Darunavir/r (Prezista® + Norvir ®) + preferred 2-NRTI backbone**
  - Dose in pregnancy is darunavir 600 mg + ritonavir 100 mg twice daily with food

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DHHS Perinatal Guidelines October 26, 2016 available at http:/aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed 2.1.17.

Preferred Integrase Inhibitor

- **Raltegravir (Isentress®) + preferred 2-NRTI backbone**
  - Must be dose twice daily
  - Rapid viral load reduction
  - Few drug interactions
  - Low genetic barrier to resistance

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Alternative Regimens in Pregnancy

2 NRTIs + NNRTI OR PI/r OR INSTI

NRTI = Nucleoside Reverse Transcriptase Inhibitor
NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor
PI/r = Ritonavir boosted protease inhibitor
INSTI = Integrase strand transfer inhibitor

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DHHS Perinatal Guidelines October 26, 2016 available at http:/aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf. Accessed 2.1.17.

Alternative 2-NRTI Backbone

- **Zidovudine/Lamivudine (Combivir®)**
  - Twice daily administration
  - Increased risk for hematologic toxicities

Alternative PI Regimen

- **Lopinavir/r (Kaletra®) + preferred 2 NRTI backbone**
  - Frequently causes nausea
  - Twice daily administration required/high pill burden
    - 2 tablets BID with increase to 3 tablets BID in 2nd & 3rd trimester

Alternative Integrase Inhibitor Regimen

- **Dolutegravir (Tivicay®) + preferred two-NRTI backbone**
  - Limited data in pregnancy, but no safety problems identified to date
  - High genetic barrier to resistance
  - Can take with or without food

Alternative NNRTI Regimens

- **Efavirenz (Sustiva®) + preferred 2-NRTI backbone**
  - Birth defects in primates; human risk less clear
  - Neuropsychiatric side effects
  - Once daily, single tablet combination available (Atripla®)
- **Rilpivirine (Edurant®) + preferred 2-NRTI backbone**
  - Available as fixed drug single tablet regimen with tenofovir df/emtricitabine (Complera®)
  - Contraindicated with proton pump inhibitors, separate from other acid reducing agents
  - Must take with a meal for absorption
  - Not recommended if pre-treatment HIV viral load > 100,000 copies/mL or CD4 cell count < 200 cells/mm^3

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Poll

What if a woman with HIV infection becomes pregnant while already on antiretrovirals that are fully suppressing her HIV viral load?

a) Regimen must be changed to a "preferred regimen"
b) An HIV resistance test should be done
c) She can stay on her regimen as long as it is safe and effective in pregnancy and working for her
d) Antiretrovirals should be stopped to prevent injury to the baby

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ARVs Not Recommended In Pregnancy

- Stribild® (TDF/FTC/EVG/c) or Genvoya® (TAF/FTC/EVG/c)
  - Concern for viral breakthrough
  - If continue, monitor viral load closely and consider therapeutic drug monitoring
- Tenofovir alafenamide – data lacking in pregnancy
- Stavudine (d4T)
- Didanosine (ddI)
- Treatment dose ritonavir (600 mg BID)

Toxicity Risks

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Monitoring HIV in Pregnancy

- HIV viral load testing
  - Initial visit (AI)
  - 2-4 weeks after starting or changing ART (BI)
  - Monthly until HIV viral load is below limit of detection of test (BIII)
  - Every 3 months during pregnancy (BIII)
  - 34-36 weeks' gestation to inform delivery decisions (AIII)
- Antiretroviral resistance testing
  - Prior to starting ART if never on treatment (AIII)
  - Prior to changing regimen if HIV RNA above threshold for resistance testing (> 500 to 1,000 copies/mL) (AIII)

What if virologic suppression is not attained?

1. Test for drug resistance
2. Assess drug adherence, tolerability, dosing, potential problems with absorption, lack of attention to food requirements
3. Consideration of ART modification

Adherence to ART, labs and appointments (both OB and HIV care) are critical to success in preventing mother to child transmission!

Case

- DH is a 32 year old woman in her 28th week of gestation who has a history of AIDS with multiple antiretroviral resistance mutations due to prior medication nonadherence
- For the last 5 years has been very adherent to her regimen of darunavir 600 mg twice daily + ritonavir 100 mg twice daily + tenofovir DF/emtricitabine one tablet daily + raltegravir 400 mg twice daily
- Viral load 600 copies/mL

Case

- Genotype done and patient has developed new resistance to raltegravir
- Raltegravir discontinued and dolutegravir 50 mg twice daily added to regimen
- Viral load 2 weeks later was < 20 copies/mL
- Baby born healthy without HIV infection on subsequent testing
- Mother remains adherent to her regimen with subsequent fully suppressed HIV viral load

Management During Labor

- Guidelines recommend against the following unless clear obstetric indication:
  - Artificial rupture of membranes
  - Invasive fetal scalp monitoring with scalp electrodes
  - Operative delivery with forceps or vacuum extractor
  - Episiotomy

Virologic failure near delivery

- HIV RNA > 1,000 copies/mL or unknown viral load
  - Scheduled cesarean section at 38 weeks (AI)
  - Intravenous zidovudine (AI)

Types of ART for Newborns With Perinatal HIV Exposure	
Antiretroviral Prophylaxis	ART for newborns without confirmed HIV AZT + one or two other antiretroviral drugs
Empiric Therapy	Newborn at high risk of HIV acquisition Three drug combination regimen
HIV Therapy	Infants with confirmed HIV Three drug combination regimen Therapy is lifelong

Recommended Virologic Testing for Infants Exposed to HIV Based on Transmission Risk

	Birth	2-3 wk	4-8 wk	8-10 wk	4-6 mos
Low Risk		NAT	NAT		NAT
Higher Risk	NAT	NAT	NAT	NAT	NAT

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Breastfeeding and HIV Infection

- Risk of HIV transmission occurs throughout the breastfeeding period
- If no infant antiretroviral prophylaxis (or maternal ART)
  - Highest risk first 4-6 weeks of life (0.7% to 1% per week)
  - Late postnatal infection risk after 4-6 weeks is 0.17% per week

AAP Committee on Pediatric AIDS. Pediatrics 2013;131:391-396.

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Factors Increasing Risk of HIV Transmission Through Breastfeeding

- High maternal plasma and human milk viral load
- Low maternal CD4 cell count
- Longer duration of breastfeeding
- Breast abnormalities
- Oral lesions in infant
- Mixed breastfeeding and formula feeding
- Abrupt weaning
- Mother not on suppressive ART and/or infant not on Prophylactic ART throughout lactation (+ 6 weeks after ending)

AAP Committee on Pediatric AIDS. Pediatrics 2013;131:391-396.

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Why do we recommended avoidance of breastfeeding in the US?

1. 1% to 5% risk of transmission of HIV though exposure to breastmilk containing HIV even if mother on ART and baby on PEP
2. Transmission possible even if mother's plasma HIV RNA is undetectable
3. Maternal prophylaxis may be less effective if started late in pregnancy or during postpartum period
4. Potential toxicity of ARVs in infant exposed to drugs through breast milk
5. Access to clean water and affordable replacement feeding exists in the US

AAP Committee on Pediatric AIDS. Pediatrics 2013;131:391-396.

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What about premastication?

- 2008 US study:14% of mothers of healthy babies premasticated food for their child
- Late HIV transmission has been documented through infant consumption of premasticated food given by caregivers with HIV infection

Fein SB, et al. Pediatrics. 2008;122(suppl 2):S91-S97.
Gaur AH, et al. Pediatrics. 2009 Aug;124(2):658-66.

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Missed Opportunities for Preventing Perinatal Transmission of HIV: Florida 2007 – 2014

- Retrospective review of de-identified data from Florida's Enhanced HIV/AIDS Reporting System (eHARS)
- 70/4337 (1.6%) known singleton births exposed to maternal HIV infection were perinatally infected
- Among the infected maternal-infant dyads **over 1/3 of mothers used illegal drugs** or **acquired an STD during pregnancy**

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Trepka MJ et al. Southern Med J 2017 Feb;110(2):11-128. PMID: 28158882

Missed Opportunities for Preventing Perinatal Transmission of HIV: Florida 2007 – 2014

- Relative Risk of Perinatal Transmission
  - **Maternal HIV Diagnosis during labor and delivery**
    - RR = 5.66, (95% CI 2.31-13.91) (compared with prenatal diagnosis)
  - **Maternal HIV Diagnosis after birth**
    - RR = 26.50, (95% CI 15.44-45.49)
- Among 29 women whose HIV infection was not known before pregnancy and whose child was perinatally infected
  - 18 were not diagnosed during pregnancy
  - 12 of the 18 had **evidence of Acute HIV Infection**
  - 6 of the 18 had **no prenatal care**

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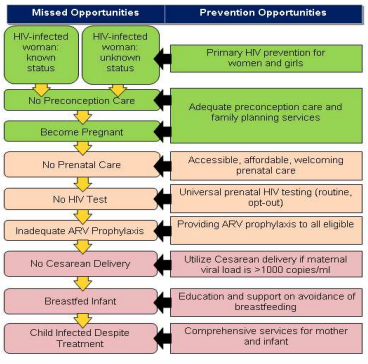
Trepka MJ et al. Southern Med J 2017 Feb;110(2):11-128. PMID: 28158882



Framework for elimination of perinatal HIV transmission

Framework graphic from http://www.cdc.gov/hiv/group/gender/pregnantwomen/emct.html

10 Action Steps for a Healthy Baby During an HIV Affected Pregnancy

1. Review **HIV status** (viral loads, CD4 counts, STIs, etc.)
2. Review **health of pregnancy** status (previous pregnancies, deliveries, additional health concerns and healthy steps)
3. Provide Understanding and Support for **Disclosure**
4. Create a **pregnancy plan** with the mother (family)
5. **Problem solve effective therapy and optimal adherence**
6. Initiate/continue an **ARV regimen per guidelines**
7. **Confirm adequate response** to ARVs in 2-4 weeks
8. **Monitor adherence and response** at least every 3 months and at least in each trimester (especially at 34-36 weeks)
9. Create a **delivery plan** based on all the data – review it serially
10. **Implement** the delivery plan and follow-up for mother and infant

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Slide courtesy of Robert Lawrence, MD

Perinatal HIV/AIDS

Rapid perinatal HIV consultation from practicing providers

- HIV testing in pregnancy
- Treating HIV-infected pregnant women
- Preventing transmission during labor and delivery and the post-partum period
- HIV-exposed infant care

Call for a Phone Consultation

(888) 448-8765

24 hours,

Seven days a week

CALL

http://nccc.ucsf.edu/clinician-consultation/perinatal-hiv-aids/

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