HIV MANAGEMENT IN PRIMARY CARE

Continuing Education Seminar

St. Agnes Hospital | October 27, 2018

Sponsored by

MARYLAND DEPARTMENT OF HEALTH
Medicaid Pharmacy Program

MARYLAND
Department of Health

Continuing Medical Education (CME) &
Pharmacy Continuing Education (CE) Seminar

HIV Management in Primary Care
on
October 27, 2018
at
Alagia Auditorium, St. Agnes Hospital

7:30 am – Breakfast and Registration	
8:30 am – Introductions	Maryland Medicaid Pharmacy Program
8:45 am – HIV Treatment in 2018	Devang Patel, MD, MS Assistant Professor UM School of Medicine
9:45 am – Antiretroviral Pipeline Update	Neha Sheth Pandit, PharmD, AAHIVP, BCPS Associate Professor UM School of Pharmacy
10:45 am – Break	
11:00 am – Antiretrovirals: Medication Errors and Medication Safety	Mary Banoub, PharmD Clinical Pharmacist, Infectious Disease UMMC
12:00 pm – Psychiatric Aspects of HIV Care	Charles Robinson, MD Assistant Professor UM School of Medicine
1:00 pm – Closing Remarks	Maryland Medicaid Pharmacy Program

The views and opinions expressed by the speakers are not necessarily the views and opinions of The State of Maryland Department of Health.

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Program Disclosure:
This program is supported by funded research.

Activity Type: Knowledge-Based

HIV Treatment in 2018

Devang Patel, MD

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

INSTITUTE OF HUMAN VIROLOGY

1

Disclosures

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2

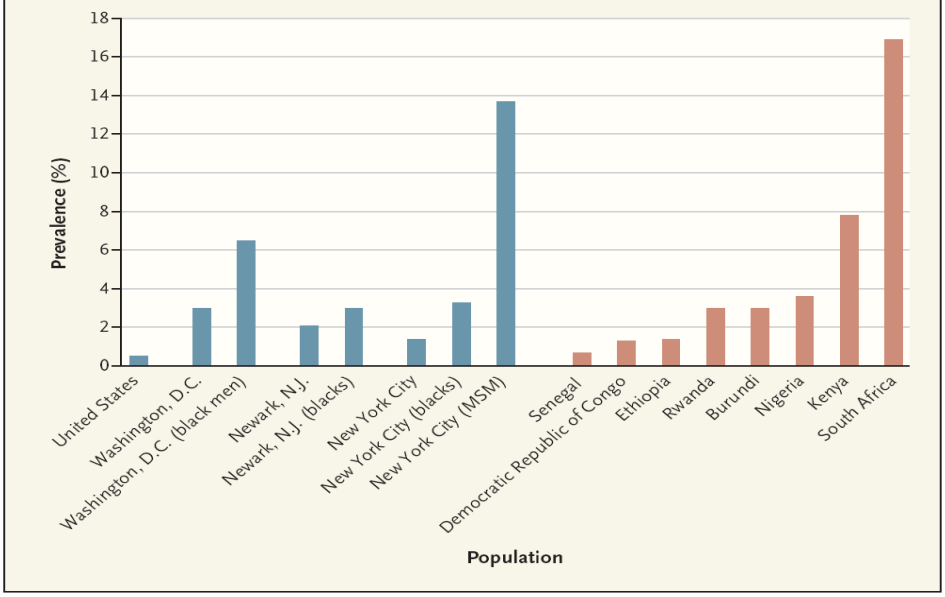
Objectives

- Understand the current HIV epidemic as it pertains to Baltimore and Maryland
- Review current ART options available for treatment of HIV
- Discuss the rationale behind current treatment guidelines from DHHS.

3

The Epidemic

4

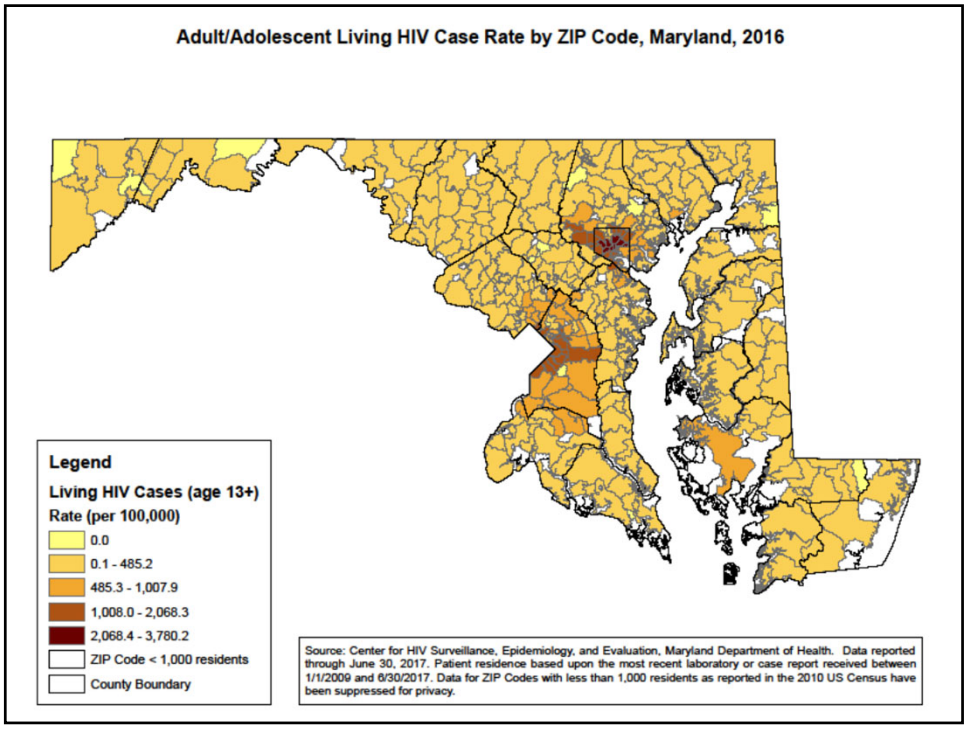


HIV Prevalence in Adults from Selected Countries in Sub-Saharan Africa and Subpopulations in the United States.

5

AIDS in America — Forgotten but Not Gone. El-Sadr et al. NEJM 2010

5



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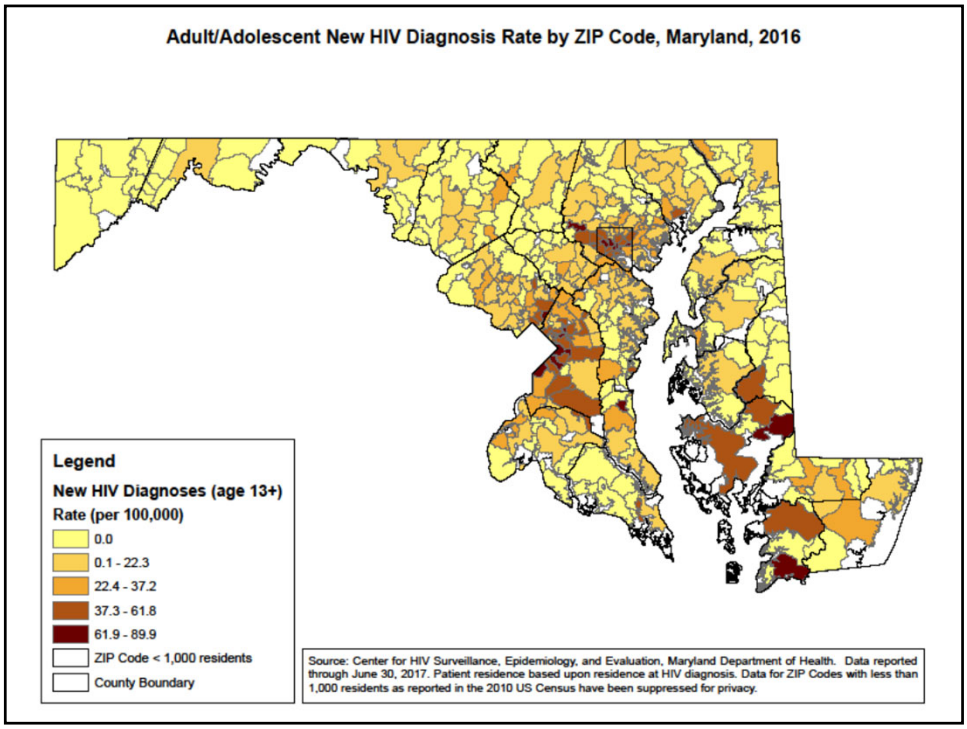
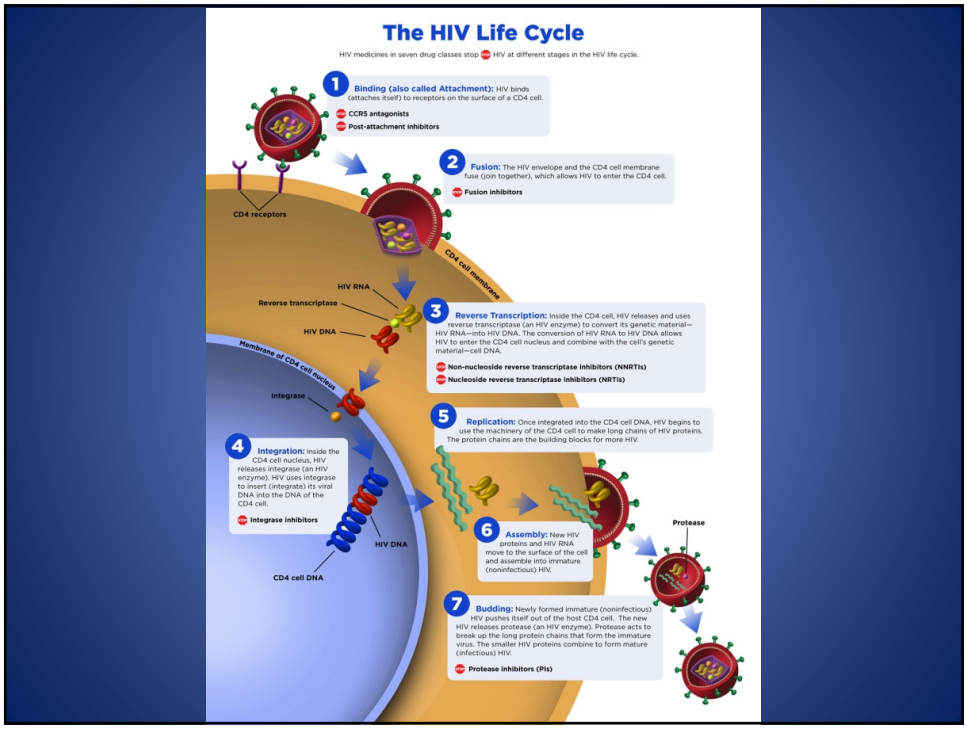


7

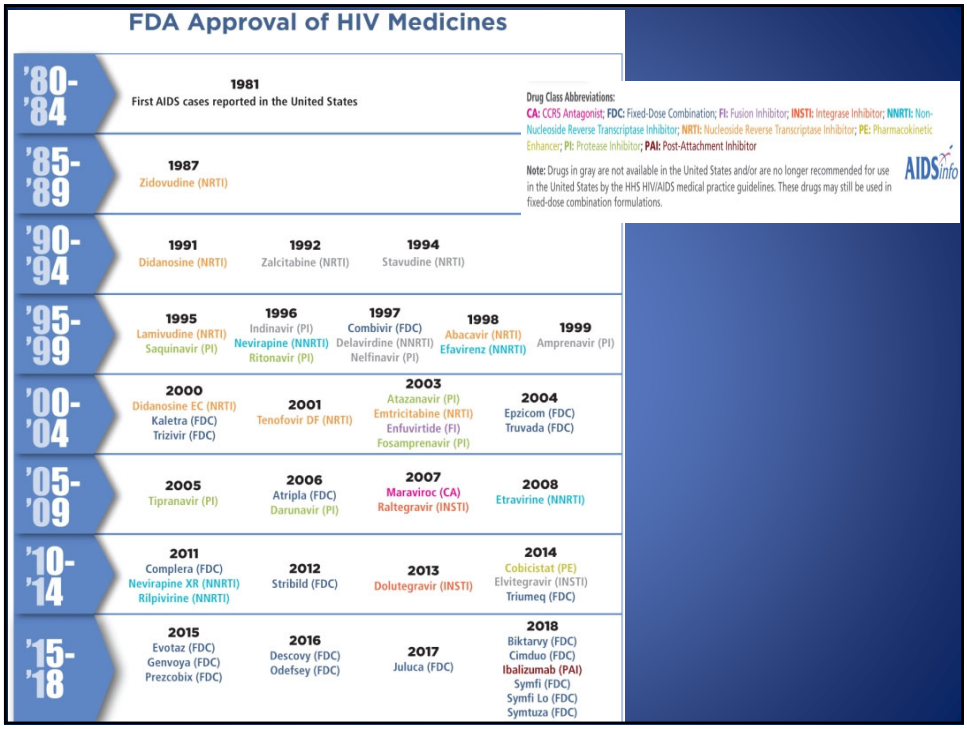
Evolution of HIV Treatment Guidelines Who to Treat

- 2004 IAS Guidelines
  - Treat CD4 count below 200
- 2006 DHHS Guidelines
  - Should be offered to those between 200-350
- 2012 DHHS Guidelines
  - Treat all regardless of CD4 count

8


The HIV Life Cycle
HIV medicines in seven drug classes stop HIV at different stages in the HIV life cycle.
1 Binding (also called Attachment): HIV binds (attaches itself) to receptors on the surface of a CD4 cell.
CCR5 antagonists
Post-attachment inhibitors
CD4 receptors
2 Fusion: The HIV envelope and the CD4 cell membrane fuse (join together), which allows HIV to enter the CD4 cell.
Fusion inhibitors
CD4 cell membrane
HIV RNA
Reverse transcriptase
HIV DNA
3 Reverse Transcription: Inside the CD4 cell, HIV releases and uses reverse transcriptase (an HIV enzyme) to convert its genetic material—HIV RNA—into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell's genetic material—cell DNA.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
Nucleoside reverse transcriptase inhibitors (NRTIs)
Membrane of CD4 cell nucleus
Integrase
4 Integration: Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.
Integrase inhibitors
HIV DNA
CD4 cell DNA
5 Replication: Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV.
6 Assembly: New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature (noninfectious) HIV.
Protease
7 Budding: Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature (infectious) HIV.
Protease inhibitors (PIs)

9


FDA Approval of HIV Medicines
'80-'84
1981
First AIDS cases reported in the United States
'85-'89
1987
Zidovudine (NRTI)
'90-'94
1991
Didanosine (NRTI)
1992
Zalcitabine (NRTI)
1994
Stavudine (NRTI)
'95-'99
1995
Lamivudine (NRTI)
Saquinavir (PI)
1996
Indinavir (PI)
Nevirapine (NNRTI)
Ritonavir (PI)
1997
Combivir (FDC)
Delavirdine (NNRTI)
Nelfinavir (PI)
1998
Abacavir (NRTI)
Efavirenz (NNRTI)
1999
Amprenavir (PI)
'00-'04
2000
Didanosine EC (NRTI)
Kaletra (FDC)
Trizivir (FDC)
2001
Tenofovir DF (NRTI)
2003
Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir (PI)
2004
Epzicom (FDC)
Truvada (FDC)
'05-'09
2005
Tipranavir (PI)
2006
Atripla (FDC)
Darunavir (PI)
2007
Maraviroc (CA)
Raltegravir (INSTI)
2008
Etravirine (NNRTI)
'10-'14
2011
Complera (FDC)
Nevirapine XR (NNRTI)
Rilpivirine (NNRTI)
2012
Stribild (FDC)
2013
Dolutegravir (INSTI)
2014
Cobicistat (PE)
Elvitegravir (INSTI)
Triumeq (FDC)
'15-'18
2015
Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)
2016
Descovy (FDC)
Odefsey (FDC)
2017
Juluca (FDC)
2018
Biktarvy (FDC)
Cimduo (FDC)
Ibalizumab (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Drug Class Abbreviations:
CA: CCR5 Antagonist; FDC: Fixed-Dose Combination; FI: Fusion Inhibitor; INSTI: Integrase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PE: Pharmacokinetic Enhancer; PI: Protease Inhibitor; PAI: Post-Attachment Inhibitor
Note: Drugs in gray are not available in the United States and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.
AIDSinfo

10

Initial Therapy in Previous Guidelines

2 NRTIs + Something

11

Initial Therapy

- 2 NRTIs
  - Abacavir + Lamivudine (Epzicom)
  - Tenofovir + Emtricitabine (Truvada)
- Something
  - NNRTI
    - Efavirenz (combined with Truvada to make Atripla)
    - Etravirine (Intelence)
    - Rilpivirine (combined with Truvada to make Complera)
  - Boosted Protease Inhibitors
    - Lopinavir (Kaletra)
    - Atazanavir (Reyataz)
    - Darunavir (Prezista)
  - CCR5 antagonist
    - Maraviroc (Selzentry)

12

ART advances from 2010 to now

- Integrase Inhibitors
- Cobicistat as a boosting agent
- TAF replaced TDF
- Focus on Single-Tablet Regimens (STR)
- 2 drug regimens

13

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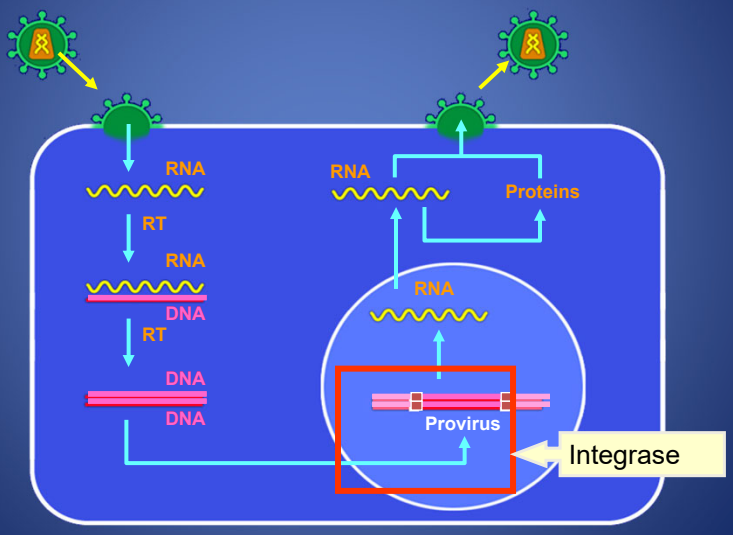
14

Integrase Inhibitor



15

Currently Approved Integrase Inhibitors (INSTIs) in the U.S.

Drug	Other Names	Year Approved
Raltegravir	(Isentress)	2007
Elvitegravir (STR with TAF/FTC and cobicistat)	(Genvoya)	2012
Dolutegravir	(Tivicay)	2013
Bictegravir (STR with TAF/FTC)	(Biktarvy)	2018

16

Raltegravir Summary: Advantages and Disadvantages

Advantages	Disadvantages
▪ INSTI with longest track record of safety and efficacy—approved in 2007 ▪ Noninferior to EFV in initial therapy ▪ Fewer CNS adverse effects, less rash, and better lipids than EFV ▪ Few drug–drug interactions ▪ No food effect	▪ Twice-daily dosing ▪ No FDC available or planned ▪ Risk of resistance at VF, especially in treatment-experienced pts ▪ When VF failure occurs with resistance, 2-class resistance is common

17

Elvitegravir Summary: Advantages and Disadvantages

Advantages	Disadvantages
▪ Noninferior to EFV and ATV/RTV in initial therapy ▪ Fewer CNS adverse effects, less rash, and better lipids than EFV ▪ Less jaundice than ATV/RTV ▪ Appears to be effective switch regimen for patients on first-line RAL ▪ Noninferior to RAL in treatment-experienced patients	▪ Not recommended for patients with eGFR < 70 mL/min ▪ Must be taken with food ▪ Cobicistat inhibits tubular secretion of creatinine, increasing Cr levels ▪ More nausea than EFV ▪ Many COBI-related drug–drug interactions

18

Dolutegravir Summary: Advantages and Disadvantages

Advantages	Disadvantages
▪ FDC with ABC/3TC known as Triumeq ▪ **Noninferior to RAL and superior to EFV and DRV/RTV** ▪ Fewer CNS and rash events vs EFV ▪ When VF occurs, no integrase resistance mutations as yet detected in treatment-naive patients ▪ Few drug–drug interactions ▪ Can be taken with or without food	▪ Inhibits tubular secretion of creatinine, increasing Cr levels ▪ Reports of neuropsychiatric side effects

19

FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

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[05-18-2018]

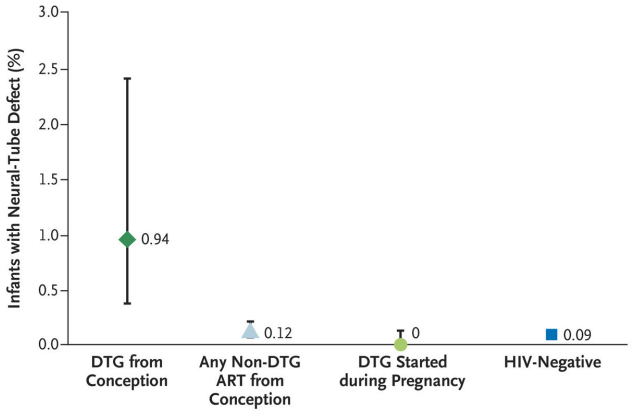
Safety Announcement

The U.S. Food and Drug Administration (FDA) is alerting the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

20

CORRESPONDENCE

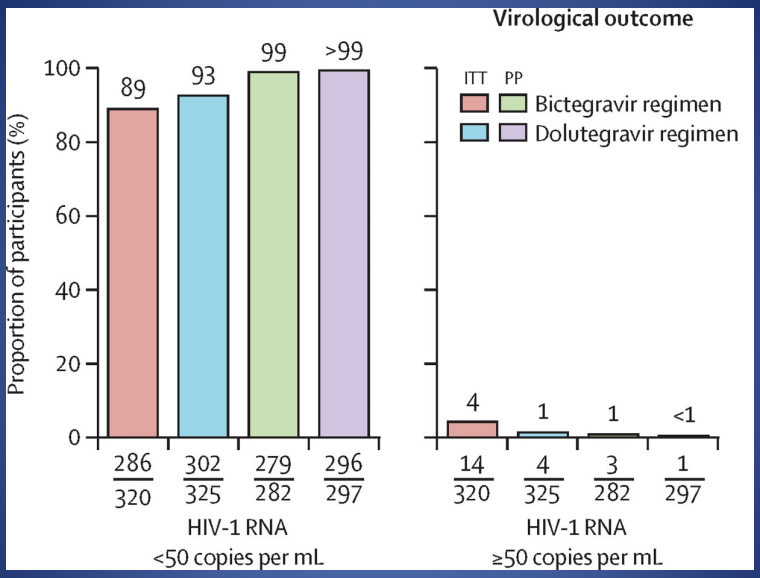
Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception



	DTG from Conception	Any Non-DTG ART from Conception	DTG Started during Pregnancy	HIV-Negative
No. of infants with defect	4	14	0	61
No. of exposures	426	11,300	2812	66,057
Percent with defect (95% CI)	0.94 (0.37 to 2.4)	0.12 (0.07 to 0.21)	0.0 (0.0 to 0.13)	0.09 (0.07 to 0.12)
Difference in prevalence (95% CI) — percentage points	Reference	−0.82 (−0.24 to −2.3)	−0.94 (−0.35 to −2.4)	−0.85 (−0.27 to −2.3)

21

Bictegravir vs Dolutegravir



THE LANCET
Volume 390, Issue 10107, 4–10 November 2017, Pages 2073-2082

22

ART advances from 2010 to now

- Integrase Inhibitors
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- 2 drug regimens

23

Ways to Boost Protease Inhibitors

- Inhibitors of Cytochrome P450, Family 3, subfamily A
  - CYP3A
- Ritonavir (low dose)
  - FDC with Lopinavir (Kaletra)
- Cobicistat
  - Fewer drug-drug interactions
  - Less metabolic side effects
  - Can cause minor elevation in Cr
  - FDC with Darunavir (Prezcobix)
  - FDC with Atazanavir (Evotaz)

24

ART advances from 2010 to now

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25

Tenofovir Alefenamide (TAF)

- Prodrug of tenofovir
- Fewer renal and bone effects
- Lower dose (more intracellular) – SMALLER PILLS
- Non-inferior to TDF
- Only available in combination form

• TDF/FTC (Truvada)	-> TAF/FTC (Descovy)
• TDF/FTC/EFV (Atripla)	-> No TAF formulation
• TDF/FTC/RPV (Complera)	-> TAF/FTC/RPV (Odefsey)
• TDF/FTC/EVG/cobi (Stribild)	-> TAF/FTC/EVG/cobi (Genvoya)

26

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- 2 drug regimens

27

28

Antiretroviral drugs 2018/19 www.i-Base.info

Drug names		Recommended adult dose *	Total daily pills
Fixed dose combinations	0 5 10 15 20 mm *Approximate to actual size.*		
Atripla (efavirenz + emtricitabine + tenofovir DF)		One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Biktarvy (bictegravir + TAF + emtricitabine) §		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Complera (rilpivirine + emtricitabine + tenofovir DF)		One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir + abacavir + lamivudine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir + cobicistat + emtricitabine + TAF)		One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir DF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Symtuza (darunavir + cobicistat + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Juluca (dolutegravir + rilpivirine) §		One tablet, once-daily, take with food. See info on separate drugs.	1

29

ART advances from 2010 to now

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30

2 Drug Regimens

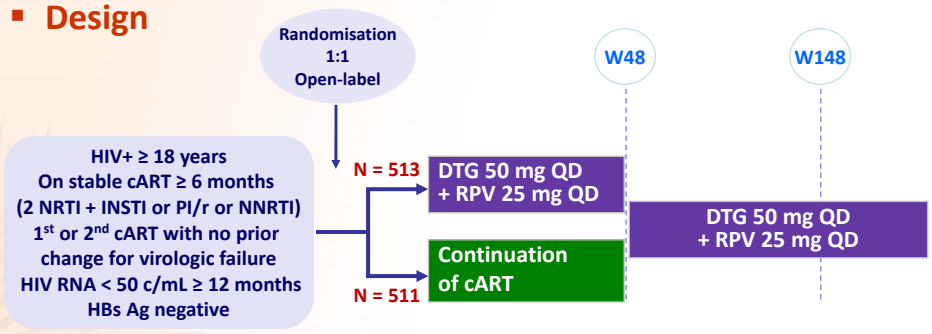
- Dolutegravir + Rilpivirine (FDA approved as Juluca)
- Dolutegravir + 3TC
- Cabotegravir + Rilpivirine

31

SWORD-1 & 2 Studies: Switch to DTG + RPV

ARV-trials.com

- **Design**



- **Endpoint**
  - Primary: proportion of patients maintaining HIV RNA < 50 c/mL at W48 (ITT-exposed, snapshot) ; non-inferiority if lower margin of a two-sided 95% CI for the difference = - 8% for pooled studies (- 10% for each individual study)

SWORD

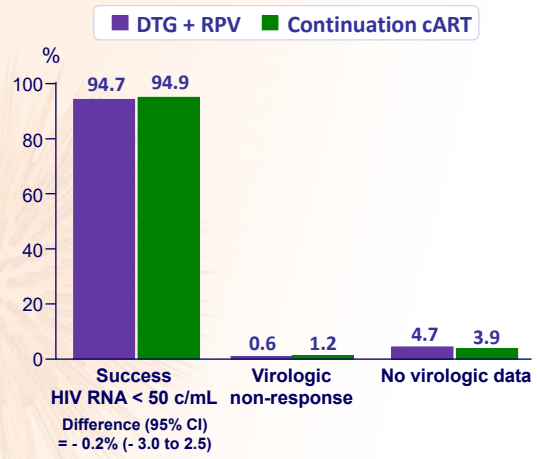
Llibre JM. CROI 2017, Abs. 44LB

32

SWORD-1 & 2 Studies: Switch to DTG + RPV

ARV-trials.com

Virologic outcome at W48 (ITT-E, snapshot)



Other virologic results at W48

- HIV RNA < 50 c/mL (ITT-E snapshot)
  - SWORD-1
    - 95% DTG + RPV
    - 96% continuation cART
    - Adjusted ≠: - 0.6% (95% CI: - 4.3 to + 3.0)
  - SWORD-2
    - 94% DTG + RPV
    - 94% continuation cART
    - Adjusted ≠: 0.2% (95% CI: - 3.9 to + 4.2)
- Confirmed virologic failure: HIV RNA ≥ 50 c/mL, retest ≥ 200 c/mL
  - DTG + RPV, N = 2
    - Emergence of NNRTI resistance mutation (K101K/E)
  - Continued cART, N = 2
    - No mutations

SWORD

Llibre JM. CROI 2017, Abs. 44LB

33

Current DHHS Guidelines

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

- INSTI + 2 NRTIs:
  - DTG/ABC/3TC **(AI)**—if HLA-B*5701 negative
  - DTG + tenofovir/FTC (**AI** for both TAF/FTC and TDF/FTC)
  - BIC/tenofovir/FTC (**AI** for both TAF/FTC and TDF/FTC)
  - EVG/c/tenofovir/FTC (**AI** for both TAF/FTC and TDF/FTC)
  - RAL + tenofovir/FTC (**AI** for TDF/FTC, **AII** for TAF/FTC)

34

Current DHHS Guidelines

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

- INSTI + 2 NRTIs:
- DTG/ABC/3TC -Triumeq
- DTG + TAF/FTC
- BIC/TAF/FTC - Biktarvy

35

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir[b]/FTC[a] (**AI** for DRV/r and **AII** for DRV/c)
- (ATV/c or ATV/r) + tenofovir[b]/FTC[a] **(BI)**
- (DRV/c or DRV/r) + ABC/3TC[a] **—if HLA-B*5701—negative (BII)**
- (ATV/c or ATV/r) + ABC/3TC[a] **—if HLA-B*5701—negative and HIV RNA <100,000 copies/mL** (**CI** for ATV/r and **CIII** for ATV/c)

NNRTI + 2 NRTIs:

- EFV + tenofovir[b]/FTC[a] (**BI** for EFV/TDF/FTC and **BII** for EFV + TAF/FTC)
- RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**

INSTI + 2 NRTIs:

- RAL[c] + ABC/3TC[a] **(CII)—if HLA-B*5701—negative and HIV RNA < 100,000 copies/mL**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d]

- DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**
- LPV/r + 3TC[a] (BID)[e] **(CI)**

36

Patients of Child-Bearing Potential

- Concerns with Dolutegravir and potentially Bictegravir

ARV Drug Class	ARV	Considerations
INSTI	Raltegravir (RAL)	• Before pregnancy, dose at 1200 mg (as two 600-mg tablets) once daily or 400 mg BID. • During pregnancy, dose at 400 mg BID. • Dose separately from iron supplement. • Note: At this time, it is not known if the potential effect of DTG on the fetus is specific to DTG or whether it represents an INSTI class effect. This uncertainty should be acknowledged and discussed with the patient.
Protease inhibitor (PI)	Atazanavir/ ritonavir (ATV/RTV)	• ATV concentration may be affected by acid-lowering agents; careful attention should be paid to this interaction in those taking or needing acid-lowering therapy during pregnancy.
	Darunavir/ ritonavir (DRV/RTV)	• Before pregnancy (if there is no known PI resistance), dose at DRV/RTV 800 mg/100 mg once daily or DRV/RTV 600 mg/100 mg BID. • During pregnancy, dose at DRV/RTV 600 mg/100 mg BID.
Non-nucleoside reverse transcriptase inhibitors (NNRTI)[a]	Efavirenz (EFV)	• Primate studies have raised concerns about birth defects, but these defects have not been seen in human studies. Based on extensive experience in pregnancy, EFV is considered to be safe to use. • Screen and monitor for antepartum depression.
	Rilpivirine (RPV)	• For ARV-naive individuals, use of rilpivirine is not recommended if HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3. • Do not use with proton pump inhibitor; stagger dosing with H2 blocker.

37

Lab Monitoring at Entry to Care

- HIV serology (if not already confirmed)
- HIV drug resistance testing (HIV genotype)
- HIV viral load
- CD4 Count
- HLA B5701 (if considering ABC)
- Pregnancy test
- STI screening
  - RPR, GC
- Basic chemistry
- LFTs
- CBC
- Lipids
- A1C
- UA
- Hep B serology
- Hep C antibody
- Toxo Antibody
- Quantiferon

38

Monitoring Treatment

- VL 2-8 weeks after initiation of treatment
  - Expect a 1-2 log decline at 4 weeks
  - Most suppressed at 3-4 months
  - Resistance testing if not suppressed at 6 months
  - Can be monitored every 6 months once suppressed for 2 years
- CD4 count every 3-6 months for the 1st two years
  - For CD4 of 300-500, can be done every 6 months
  - Above 500, testing is optional

39

Monitoring Treatment

- Basic Chemistry
  - Every 3-6 months
- Lipids
  - Yearly if normal
- A1C
  - Yearly if normal
- LFTs
  - Every 3-6 months
- UA
  - Every 6 months if on TAF or TDF

40

Case 1

- 32 year old woman started on Atripla 4 months ago. Baseline VL was 100,000 and CD4 count was 350. Labs today show a VL of 90,000 and CD4 count of 270. What should do?
  - A. change regimen to Triumeq
  - B. Assess for barriers to adherence
  - C. Get a genotype
  - D. Stop ARVs

41

Case 2

- 45 year old woman who has been on Complera for 3 years who comes in for routine follow-up. VL is undetectable today as it was 3 months ago. CD4 count has decreased from 600 at last visit to 300 today. What is you next step in management?

42

Questions?

43

Antiretroviral Pipeline Update

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OCTOBER 2018

1

Disclosure

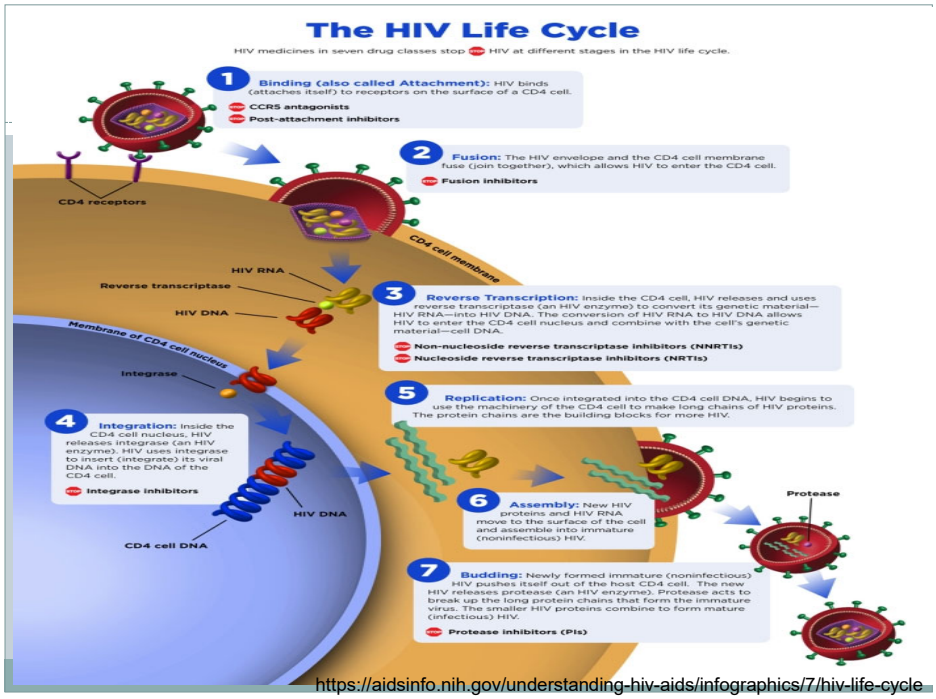
- No financial conflict
- Will discuss off-label use of medication
- This program is supported by funded research

2

Objectives

- Review new ARV classes currently under investigation
- Discuss new ARV formulations under investigation
- Assess the role of new ARV classes, medications and formulations in the HIV infected population

3



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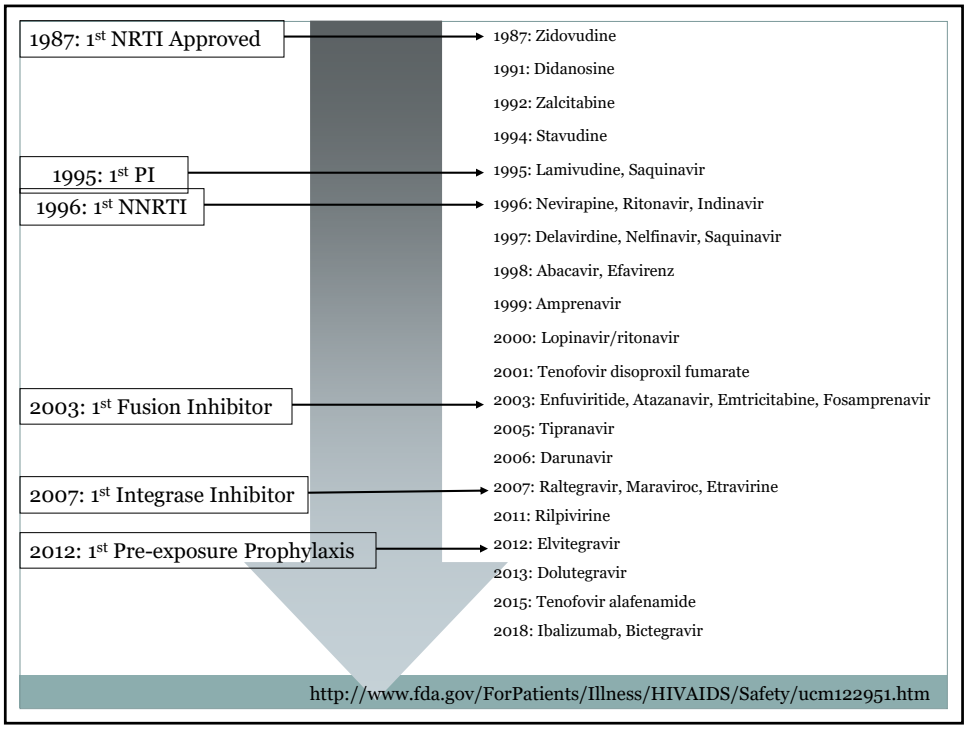

5

Changes in HIV Treatment Guidelines

- Investigational Drugs
  - NRTTI
    - EFdA
  - NNRTI
    - Doravirine
  - GP120 inhibitor
    - Fostemsavir
  - Long-acting agents
    - Rilpvirine
    - Cabotegravir
- Investigational Strategies
  - Naïve:
    - DTG+3TC
    - DRV/r +3TC
  - Latency reversing agents

6

Doravirine (DOR)

- Non-nucleoside reverse transcriptase inhibitor
- DOR 100 mg po daily
- Substrate: CYP3A4, P-gp
- Resistance
  - Minor cross resistance with RPV and EFV
  - Resistance seen with Y188L

7

DOR: DRIVE-FORWARD

- DOR vs Darunavir/r +
  - Tenofovir DF/emtricitabine (TDF/FTC) or
  - abacavir/lamivudine (ABC/3TC) po daily
- Multicenter, randomized, double-blind phase 3 trial

Drug	Week 48[1]	Week 96[2]
DOR (n=383)	80%	73.1%
DRV/r (n=383)	84%	66%
	CI: -1.6%-9.4%	CI: 0.5-13.7

[1]Molina JM et al. Lancet HIV 2018;5(5):e211-e220.
[2]Molina JM et al. AIDS 2018. Abstract LBPEB017.

8

DOR: DRIVE-AHEAD

- DOR/3TC/TDF vs EFV/FTC/TDF+
- Multicenter, randomized, double-blind phase 3 trial

Drug	Week 48	Observed Failure Approach	Baseline VL >100,000 copies/ml	>31 y/o*	≤31 y/o*
DOR (n=364)	84%	88.7%	81.2%	94.2%	83.4%
EFV (n=364)	81%	88.8%	80.8%	84.7%	92%

*Statistically significant

Orkin C et al. CROI 2018. Abstract 491.
Squires KE et al. IAS 2017. Abstract TUAB0104LB

9

DOR: Adverse Events

DRIVE-FORWARD

	DOR %	DRV/r %
Diarrhea	17	23.8
Nausea	11.7	13.6
Headache	14.9	12
Upper RTI	13.3	7.8
Hyperbilirubin	1.8	0.3
LDL (change mg/dl)	-0.4	14
Total Cholesterol (change mg/dl)	4.1	21.9
Neuropsychiatric	15.7	18.8

DRIVE-AHEAD

	DOR %	EFV %
Dizziness	8.8	37.1
Sleep disturbance	12.1	25.5
Altered mental status	4.4	8.2
LDL (change mg/dl)	-1.6	8.7

10

DOR Next Steps

A NEW DRUG APPLICATION WAS SUBMITTED FOR DOR WITH OTHER AGENTS IN ADDITION TO A FIXED-DOSE COMBINATION TABLET OF DOR/TDF/FTC. A RESPONSE IS ANTICIPATED IN OCTOBER 2018.

11

Fostemsavir (FTR)

- HIV glycoprotein 120 attachment inhibitor (gp-120)
- Prodrug of temsavir (TMR)
- FTR 600 mg po BID
- Substrate: CYP3A4 (TMR), P-gp
- Inhibitor: OATP1B1/B3, BRCP
- Resistance
  - No high level resistance was seen in naïve and experienced patients

12

FTR: BRIGHTE

- FTR vs Optimized background therapy (OBT)
- FTR monotherapy x 8 day → FTR +OBT x 96 week total
- Randomized, cohort phase 3 trial
- # of ARVs active in FTR +OBT at baseline
  - All patients resistant to ≥2 classes of ART
  - 0: 10%
  - 1: 51%
  - 2: 39%

Drug	Day 8 (Δ HIV RNA from baseline)	Week 24	
		Baseline VL <100,000	Baseline VL ≥100,000
FTR (n=203)	-0.79 (-0.88 to -0.7)	60%	38%
Placebo (n=69)	-0.17 (-0.33 to -0.01)		

Pialoux G et al. AIDS 2018. Abstract THPEB045.

13

Fostemsavir: Adverse Events

- Week 24
  - Grade 1 to 2: 91%
  - Grade 2 to 4: 18%
    - Nausea, diarrhea, headache, vomiting, fatigue, asthenia
  - Discontinuations: 6%
    - Pneumonia (30%)
  - Death: 5%
    - AIDS/IRIS-related

Pialoux G et al. Phase 3 study of fostemsavir in heavily treatmentexperienced HIV-1-infected participants: BRIGHTE week 24 subgroup analysis in randomized cohort subjects. 22nd International ADIS Conference (AIDS 2018), 23–27 July 2018, Amsterdam. Poster abstract THPEB045.

14

Ibalizumab +FTR

- Efficacy: 40 subjects:
  - Resistance seen:
    - 93% to NRTIs; 93% to NNRTIs; 88% to PIs; 68% to INSTIs
  - Exhausted ARV classes
    - 53% ≥ 3; 35% ≥ 4; 15% all
  - 43% required fostemsavir as part of treatment (17/40 patients)

Intervention/Results:

Day 0	Day 7	Day 14	Day 21	q 2wks	Week 24	Week 48
Control	IBA Loading Dose D/c other ART	Add other ART	IBA dose	IBA dose		
		83% ≥0.5 log drop 60% ≥1 log drop			43% VL ND 55% ≥1 log drop 48% ≥2 log drop	59% VL ND

Lewis S, Fessel J, Emu B, et al. Long-acting ibalizumab in patients with multi-drug resistant HIV-1: a 24 week study. Poster presented at CROI: Feb 13-16, 2017; Seattle, WA. Poster 449LB.
Emu B, Fessel J, Schrader S, et al. 48 week safety and efficacy on treatment analysis of ibalizumab in patients with multi-drug resistant HIV-1. IDWeek; Oct 4-8, 2017; San Diego, CA.

15

FTR Next Steps

FDA EXPECTED TO REVIEW A LICENSING APPLICATION IN 2019.

16

CAB: LATTE-2

- Randomized, phase 2b, open-label trial
- Oral CAB +ABC/3TC daily x 20 weeks = Induction
  - Week 16: Oral RPV was added
- If suppressed at 20 weeks (91%), then:

Drug	Week 96
Oral CAB +ABC/3TC +RPV (n=56)	84%
CAB 400 mg + RPV 600 mg IM q 4 weeks (n=115)	87%
CAB 600 mg + RPV 900 mg q 8 week (n=115)	94%

Margolis DA et al. Lancet 2017;390:1499-1510.

17

Cabotegravir (CAB)

- Integrase strand transfer inhibitor (INSTI)
- Half-life ~40 hours
- Administered sq or IM
- Substrate: UGT1A1/1A9
- Resistance
  - Reduced susceptibilities seen with major INSTI mutation (140S and 148H+/1 97A and 74M)
  - Dolutegravir and bictegravir may have higher resistance barriers

Zhang WW et al. AIDS 2018. Abstract THPDB0104.
https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/professional

18

CAB: Adverse Events

- Injection site reactions
  - mild/moderate and transient
  - 2 participants withdrew secondary to ISR
- Other AEs:
  - Nausea, nasopharyngitis, diarrhea, and headache.
- Possible drug-induced liver injury
  - 2 participants discontinued therapy and laboratory markers resolved.

Margolis DA et al. Lancet 2017;390:1499-1510.

19

CAB Next Steps

FLAIR: SWITCHING TO CAB+RPV IM Q 4 WEEKS FROM A DTG BASED REGIMEN

ATLAS-M: SWITCHING TO CAB+RPV Q 4 WEEKS FROM S 3-DRUG REGIMEN

20

MK-8591(EFdA)

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Half-life of anabolite~120 hours
  - possible daily dosing with 'adherence forgiveness'
- Administered orally
- Resistance
  - Maintains susceptibility with M184V +/- E138K

Friedman E et al. CROI 2016 Abstract 437LB.
Oliveira M et al. J Antimicrob Chemother 2017;72:3008-11.

21

MK-8591(EFdA)

- EFdA administered: 0.25 mg, 0.75 mg and 5 mg (n-12)
  - All were above target concentration for efficacy
  - All remained elevated up to 30 days after treatment cessation.

Matthews RP et al. CROI 2018. Abstract 26.

22

EFdA Next Steps

BEING EVALUATED IN PHASE 2 TRIAL WITH DORAVIRINE (DOR) AND LAMIVUDINE (3TC) IN ART-NAÏVE PATIENTS TO DETERMINE APPROPRIATE DOSING.

23

Changes in HIV Treatment Guidelines

- Investigational Drugs
  - NRTTI
    - EFdA
  - NNRTI
    - Doravirine
  - GP120 inhibitor
    - Fostemsavir
  - Long-acting agents
    - Rilpvirine
    - Cabotegravir
- Investigational Strategies
  - Naïve:
    - DTG+3TC
    - DRV/r +3TC
  - Latency reversing agents

24

DTG+3TC: GEMINI 1 and 2

- Double-blind, multicenter Phase 3 trials
- ART-naïve patient with baseline HIV RNA ≤500,000 copies/ml
- New data results are being presented to FDA for prescribing information change

Drug	Week 48		
	All	Baseline HIV RNA: >100,000 copies/ml	Baseline HIV RNA: ≤100,000 copies/ml
DTG + 3TC daily (n=716)	91%	92%	91%
DTG + TDF/FTC daily (n=717)	93%	90%	94%
	CI 95%: -1.7 (-4.4, 1.1)		

Cahn P et al. AIDS 2018. Abstract TUAB0106LB.

25

Why Dolutegravir?

- Long plasma half-life = 15.3 hours
- High barrier to resistance
- Low incidence of severe toxicities
- Minimal drug-drug interactions

26

DRV/r+3TC: ANDES

- Open-label, randomized phase 4 study
- ART-naïve patient with no baseline mutations
- -1.4 (-17.2 to 14.4)

Drug	Week 48	
	All	Baseline HIV RNA: >100,000 copies/ml
DRV/r+3TC daily (n=75)	93%	91%
DRV/r+TDF/3TC (n=70)	94%	92%
CI 95%	-1.0 (-7.5 to 5.6)	-1.4 (-17.2 to 14.4)

Figueroa MI, et al. CROI 2018. Abstract 489.

27

Latency Reversing Agents (LRAs)

- 'kick and kill' strategy
  - 'kicks' latent cells into an active state
  - 'kills' the cell using immune response.
  - minimize HIV reservoirs by promotion of latent cell activation
- Histone deacetylation inhibitors and toll-like receptor agonists are two types of LRAs that are being evaluated

28

Vorinostat + Vaccine: RIVER

- Patient population
  - Primary HIV infected patients
  - MSM (92%)
- Methods
  - ART with 3 drugs including INSTI
  - Once suppressed
    - ART +Vorinostat + Vaccine (n=30)
      - Prime: ChAdV63.HIVconsv at randomization, boost: MVA.HIVconsv at Wk 8.
    - ART alone (n=30)
- Outcomes
  - Difference in mean log10 HIV-1 DNA copies/million CD4 cells at weeks 16 and 18
- Results
  - No significant difference in DNA reservoir in CD4 cells

Fidler S, et al. AIDS 2018. Abstract TUAA0202LB.

29

Objectives

- Review new ARV classes currently under investigation
  - GP-120 inhibitors
  - Latency reversing agents
  - New NRTI (NRTTIs)

30

Objectives

- Discuss new ARV formulations under investigation
  - Long acting intramuscular and subcutaneous injections

31

Objectives

- Assess the role of new ARV classes, medications and formulations in the HIV infected population
  - 2 drug regimens
  - Treatment simplification
  - Extended interval dosing
  - Multi-drug resistance

32

Antiretroviral (ARV) Drug Classes

- Nucleoside/nucleotide reverse transcriptase inhibitor (NRTIs)
  - Tenofovir disoproxil fumarate, Viread®, TDF
  - Tenofovir alafendamide, Vemlidy®, TAF
  - Emtricitabine, Emtriva®, FTC
  - Lamivudine, Epivir®, 3TC
  - Abacavir, Ziagen®, ABC
  - Zidovudine, Retrovir®, AZT
  - Didanosine, Videx EC®, ddI
  - Stavudine, Zerit®, d4T
- Non-nucleoside reverse transcriptase inhibitor (NNRTIs)
  - Efavirenz, Sustiva®, EFV
  - Rilpivirine, Edurant®, RPV
  - Nevirapine, Viramune®, NVP
  - Etravirine, Intelence®, ETV
- CCR5 Antagonists
  - Maraviroc, Selzentry®, MVC
- Fusion inhibitors
  - Enfuvirtide, Fuzeon®, EFV
- Protease inhibitors (PI)
  - Ritonavir, Norvir®, RTV
  - Atazanavir, Reyataz®, ATV
  - Atazanavir/cobicistat, Evotaz™, ATV/c
  - Darunavir, Prezista®, DRV
  - Darunavir/cobicistat, Prezcobix®, DRV/c
  - Lopinavir/ritonavir, Kaletra®, LPV/r
  - Fosamprenavir, Lexiva®, FPV
  - Nelfinavir, Viracept®, NFV
  - Indinavir, Crixivan®, IND
  - Saquinavir, Invirase®, SQV
  - Tipranavir, Aptivus®, TPV
- Integrase Inhibitors (INSTIs)
  - Raltegravir, Isentress®, RAL
  - Elvitegravir, Vitekta®, EVG
  - Dolutegravir, Tivicay®, DTG
  - Bictegravir, in Biktarvy®, BIC
- Pharmacokinetic Enhancers
  - Cobicistat, Tybost®, COBI

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

33

Combination Products

- Combivir®
  - Zidovudine 300 mg + Lamivudine 150 mg po bid
- Trizivir®
  - Zidovudine 300 mg + Lamivudine 150 mg + Abacavir 300 mg po bid
- Epzicom®
  - Lamivudine 300 mg + Abacavir 600 mg po daily
- Truvada®
  - TDF + Emtricitabine 200 mg po daily
- Descovy®
  - TAF + Emtricitabine 200 mg po daily
- Kaletra®
  - Lopinavir 100 mg + Ritonavir 50 mg po ; 2 tablets po bid

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

34

Combination Products
Single Tablet Regimens (STRs)

- Atripla®
  - TDF + Emtricitabine 200 mg + Efavirenz 600 mg po daily
- Complera®
  - TDF + Emtricitabine 200 mg + Rilpivirine 25 mg po daily
- Odefsey®
  - TAF + Emtricitabine 200 mg + Rilpivirine 25 mg po daily
- Triumeq®
  - Abacavir + Lamivudine + Dolutegravir po daily
- Stribild®
  - TDF + Emtricitabine 200 mg + Elvitegravir 150 mg + Cobicistat 150 mg po daily
- Genvoya®
  - TAF + Emtricitabine 200 mg + Elvitegravir 150 mg + Cobicistat 150 mg po daily
- Biktarvy®
  - TAF + Emtricitabine 200 mg + Bictegravir 50 mg po daily
- Juluca®
  - Dolutegravir 50 mg + Rilpivirine 25 mg po daily

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

35

Antiretroviral Pipeline Update

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OCTOBER 2018

36

UNIVERSITY of MARYLAND

Antiretrovirals: Medication Errors and Medication Safety

Mary Banoub, PharmD

1

Disclosures

- I have no relevant financial relationships or commercial interests to disclose for this presentation. This program is supported by funded research.

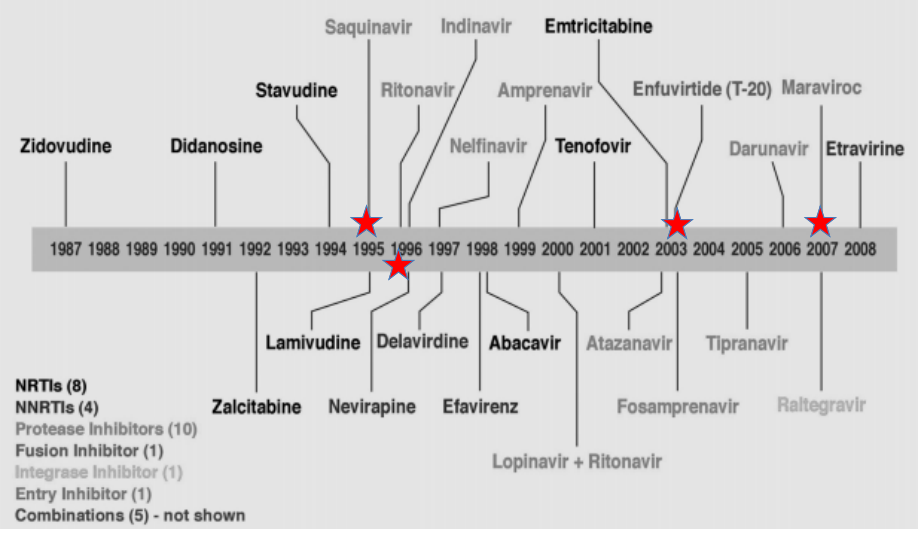
2

Objectives

- Review common antiretroviral therapy (ART) medication errors, including those related to dosage, drug interactions, and regimen selection
- Identify factors contributing to ART medication errors
- Recognize consequences of ART medication errors
- Recommend potential interventions to reduce ART medication errors

3

HIV Treatment has come a Long Way



Palmisano L, et al. Ann Ist Super Sanita. 2011;47(1):44-8.

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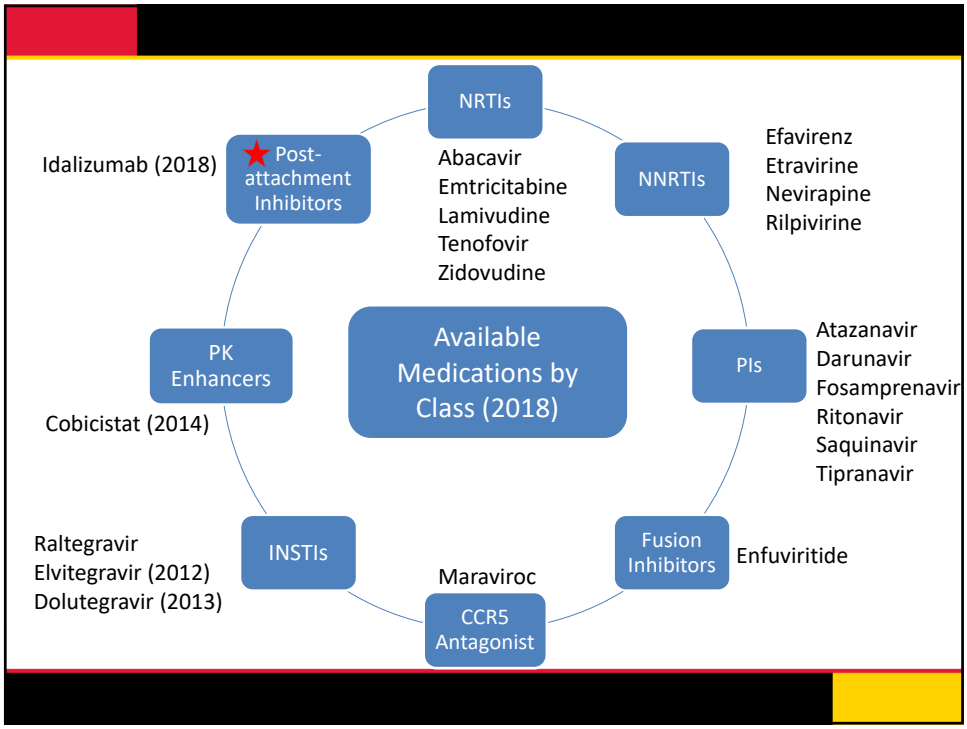

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Combination Tablets (2018)

Generic	Trade
Zidovudine 300 +Abacavir 300 + lamivudine 150 ★	Trizivir®
Efavirenz 600+ tenofovir DF 300+ emtricitabine 200	Atripla®
Rilpivirine 25 + tenofovir DF300 + emtricitabine 200	Complera®
Elvitegravir 150 + cobicistat 150 + tenofovir DF 300 + emtricitabine 200	Stribild®
Dolutegravir 50 + abacavir 600 + lamivudine 300	Triumeq®
Elvitegravir 150 + cobicistat 150 + emtricitabine 200 + tenofovir AF 10	Genvoya®
Rilpivirine 25 + tenofovir AF 25 + emtricitabine 200	Odefsey®
Dolutegravir + rilpivirine	Juluca ®
Bictegravir 50 + tenofovir AF 25 + emtricitabine 200	Biktarvy ®
Darunavir 800 + cobicistat 150	Prezcobix®
Atazanavir 300 + cobicistat 150	Evotaz®
Zidovudine 300 + lamivudine 150 ★	Combivir®
Abacavir 600 + lamivudine 300	Epzicom®
Tenofovir DF 300 + emtricitabine 200	Truvada®
Tenofovir AF 25 + emtricitabine 200	Descovy®

Complete Regimens

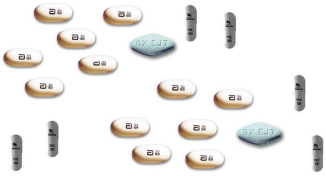
★ = BID Dosing

6

ART Today – Less Complex?

Antiretroviral therapy for HIV infection

In the 1990s



Up to 20 pills daily, taken at different intervals throughout the day

Today

As little as 1 pill per day, delivering multiple drugs

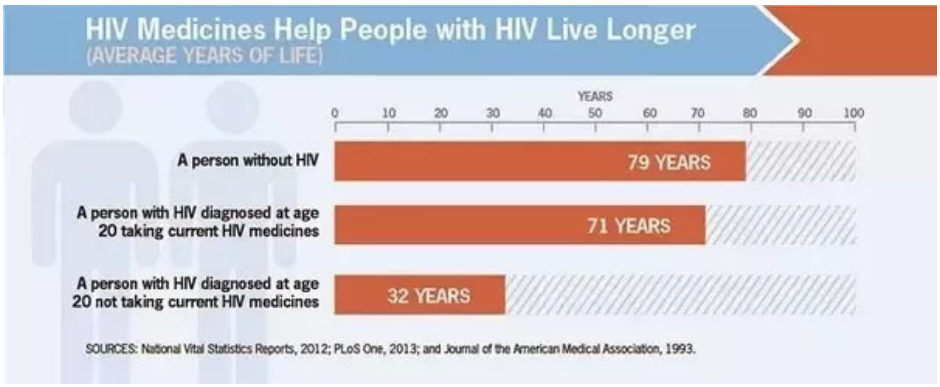
7

Considerations for ART Regimen Selection

- Treatment-naïve or experienced
- Selection of a complete/recommended regimen
  - Some combinations or components not recommended
  - Boosting
- Virologic efficacy of regimen
- Toxicity
- Pill burden
- Pill size/formulation
  - crushing
- Resistance testing results
- Dosing
  - Frequency
  - Timing
  - Renal function, hepatic function
  - Administration parameters
    - With or without food
- Drug interaction potential
- Comorbid conditions and special populations
- Access
- Cost

8

Successfully Treated HIV = Longer Life Span



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Challenges with Treating an Aging Population

- Morbidity among HIV-positive patients increasingly due to non-AIDS diseases including liver, cardiovascular, renal diseases, osteoporosis and certain cancers
  - May also be due to ART long-term side effects
  - Generally correlated with lower CD4 counts and/or detectable viral loads

Baker JV, et al. AIDS. 2008 Apr 23;22(7):841-8.

10

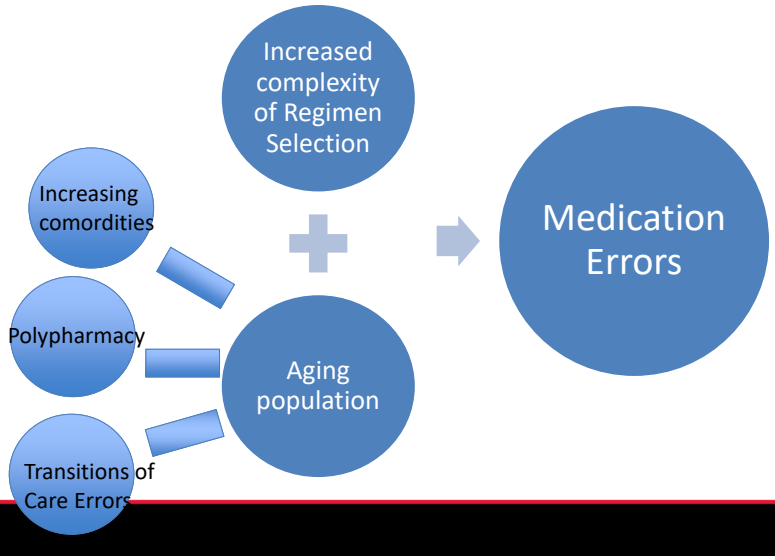
Challenges with Treating an Aging Population

- Multiple providers
  - Polypharmacy
    - Risk for drug interactions
- Transitions of care
  - Risk for a medication errors on hospital admission
    - HIV: 3.8 errors per patient
    - No HIV: 2.8 errors per patient
  - Risk for errors on discharge
    - Up to 70% of patients have medication discrepancy

Kripalani S, et al. Ann Intern Med 2012; 157:1-10
Snyder AM et al. Ann Pharmacother 2011; 45:459-68

11

A Recipe for Medication Errors



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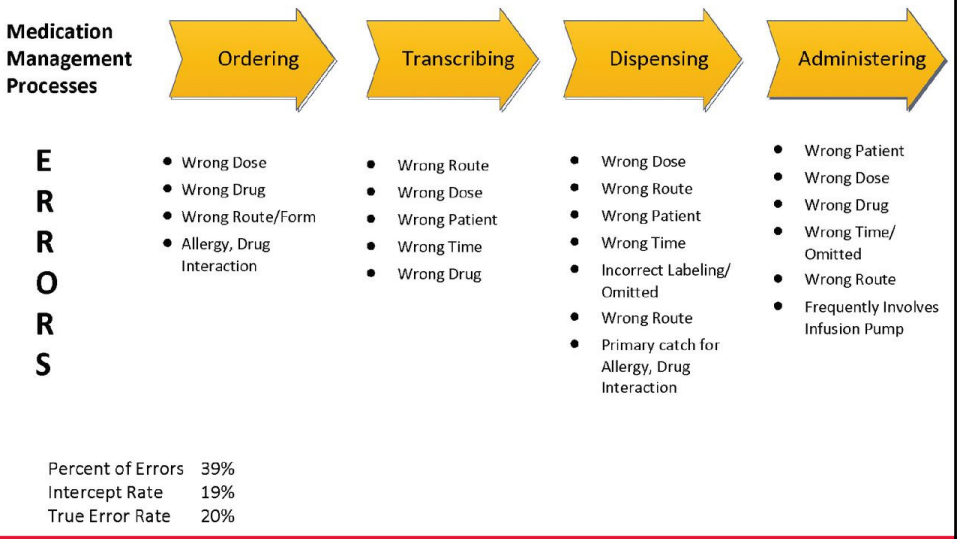
Medication Errors - Overview



Am J Health Syst Pharm. 2016 1;73(15):1144-65

13

Incidence of Errors - Inpatient

- Systematic Review of studies from 2000-2013: The overall ART medication error rate ranged between 5.8% and 86%
  - Purdy BD et al. 2000 (86 pts)
    - Errors in 5.8% of admissions to the hospital
  - Rastegar DA et al. 2006 (206 pts)
    - HIV medication errors in 26% of patients admitted
  - Pastakia SD et al. 2008 (68 pts)
    - At least one error on initial review in 72% of patients

Pastakia SD, et al. Ann Pharmacother. 2008 Apr;42(4):491-7.

14

Where are the errors occurring in Patients with HIV?

Table 2.
Types of Antiretroviral-Related Errors in Control and Intervention Groups

Error Type	Control Group	Intervention Group
Total no. errors	119	17
Prescribing, no. (%) errors	62 (52)	12 (71)
Incorrect dose or frequency	15	3
Incorrect drug	9	0
Incomplete entry	14	3
Drug interaction	11	1
Discharge summary	13	5
Dispensing, no. (%) errors	39 (33)	4 (24)
Incorrect dose or frequency	1	0
Incorrect administration time	22	1
Incorrect drug	14	0
Incomplete entry	1	0
Delay in acquisition	1	3
Outpatient documentation, no. (%) errors	18 (15)	1 (6)

Daniels LM, et al. Am J Health Syst Pharm 2012; 69:422-30.

15

Medication Errors – Types of Errors

Medication Management Processes

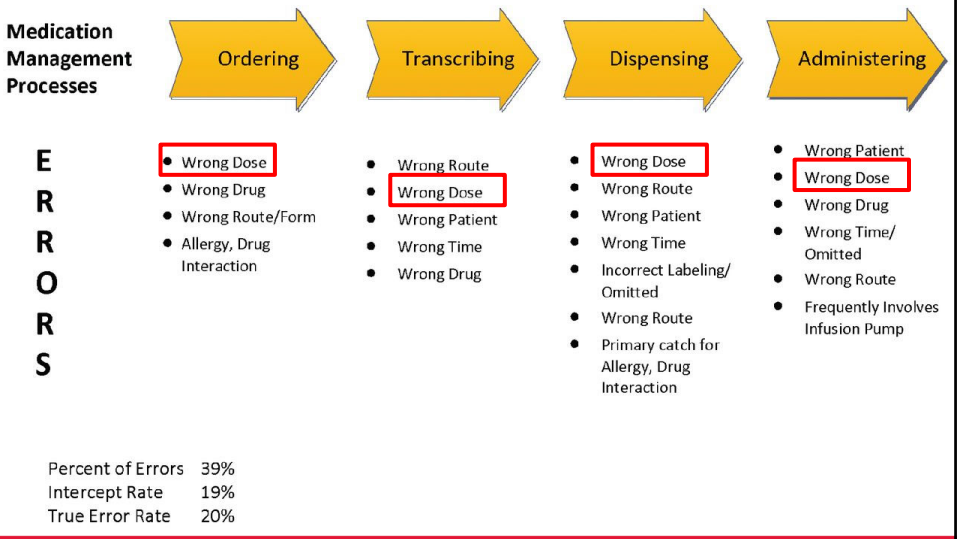
Ordering	Transcribing	Dispensing	Administering
E R R O R S			
• Wrong Dose	• Wrong Route	• Wrong Dose	• Wrong Patient
• Wrong Drug	• Wrong Dose	• Wrong Route	• Wrong Dose
• Wrong Route/Form	• Wrong Patient	• Wrong Patient	• Wrong Drug
• Allergy, Drug Interaction	• Wrong Time	• Wrong Time	• Wrong Time/ Omitted
	• Wrong Drug	• Incorrect Labeling/ Omitted	• Wrong Route
		• Wrong Route	• Frequently Involves Infusion Pump
		• Primary catch for Allergy, Drug Interaction	

Percent of Errors 39%
Intercept Rate 19%
True Error Rate 20%

Am J Health Syst Pharm. 2016 1;73(15):1144-65

16

Medication Errors – Types of Errors



Am J Health Syst Pharm. 2016 1;73(15):1144-65

17

Medication Errors - Dosage

- Adjustments based on:
  - Treatment experience
  - Drug-drug interactions
  - Drug-food interactions
  - Renal and hepatic function
    - *Most NRTIs require dose adjustment in renal dysfunction*
      - Exception: Abacavir
    - In a study evaluating NRTI dosing errors in university-based HIV clinic, renal dosing errors were the most common reason for incorrect doses (40 [75%] of 53 errors)

Willig JH, et al. Clin Infect Dis. 2007.1;45(5):658-61.

18

Medication Errors - Dosage

- Examples of dosing errors:
  - Incorrect number of tablets/capsules
  - Incorrect frequency
  - Administered without regard to meals
  - Duplication or omission of doses due to unfamiliarity with brand/generic names and co-formulated products
  - Lack of renal or hepatic adjustment

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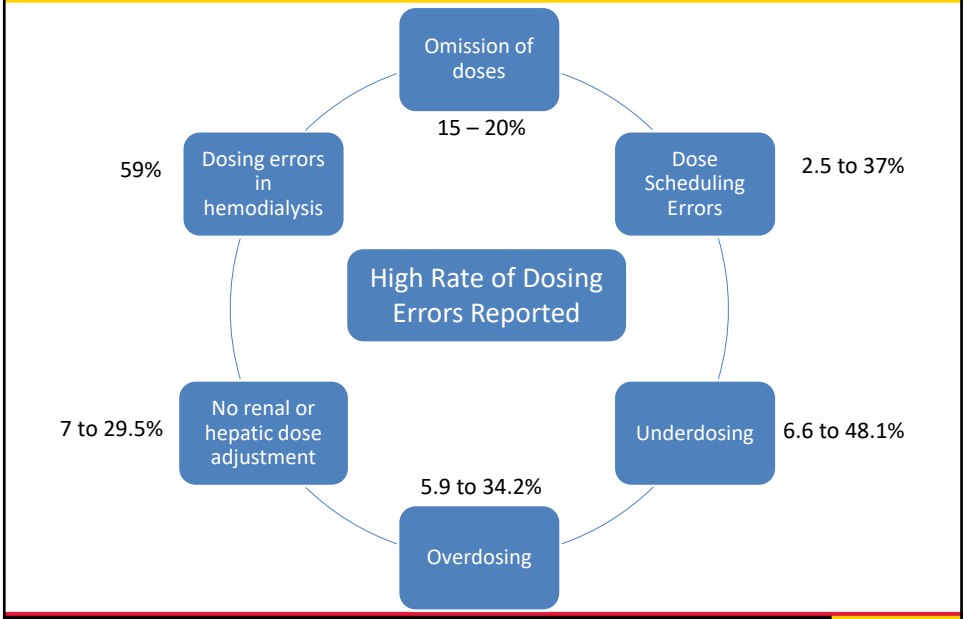


Pastakia SD, et al. Ann Pharmacother. 2008 Apr;42(4):491-7.

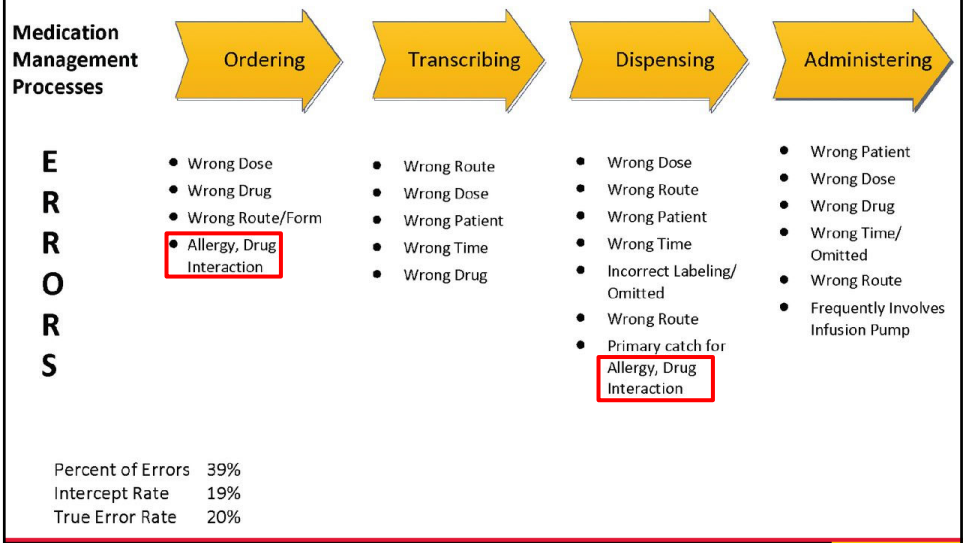
20

Examples of Dosing Errors

Antiretroviral	Dosing Error	Potential Consequences
NRTIs		
Abacavir	Prescribed at half doses; 1 tablet daily instead of 2	Dose omitted; development to resistance, VL increase
Emtricitabine or Tenofovir (TDF or TAF)	Not adjusted for renal impairment Given in conjunction with Truvada, Descovy, or TAF or TDF	Overdose, renally eliminated, may increase adverse effects Duplicate therapy; may increase ADEs
NNRTIs		
Efavirenz	No adjustment for hepatic insufficiency	Overdose: hepatically eliminated, may increase ADEs
Protease Inhibitors		
Darunavir	Prescribed as 800mg once daily in patient with darunavir resistance mutations Not given with ritonavir Not given with food	Underdosed; development to resistance, VL increase Underdose: decrease in absorption
Integrase Inhibitors		
Dolutegravir	Given as 50mg once daily in a patient with INSTI resistance	Underdosed; development to resistance, VL increase

21

Medication Errors – Types of Errors



Am J Health Syst Pharm. 2016 1;73(15):1144-65

22

Common errors – Drug Interactions

- Prevention is important to prevent:
  - Drug resistance caused by inadequate antiretroviral concentrations
  - Adverse drug effects from overexposure
- Drug-drug interactions possible amongst different ARV classes and between ARVs and other medication classes

23

Mechanisms of ARV Drug Interactions

- Drug Absorption
  - Acid-reducing agents
  - Products containing polyvalent cations
  - Drugs that induce or inhibit efflux transporter p-glycoprotein in the intestines
- Hepatic metabolism
  - Drugs that induce or inhibit 2 major enzyme systems:
    - Cytochrome P450 (CYP450, CYP3A4 most common) enzyme system
    - Uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme
- Pharmacokinetic enhancers
  - Ritonavir and Cobicistat have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters
- Others
  - Other drug transporters
  - Competitive tubular secretion

24

Protease Inhibitors – Most Commonly Implicated in Drug-Drug Interactions

- PIs are one of the most commonly implicated drug classes in medication errors overall
- In one systematic review, the most common drug interaction reported involved atazanavir and acid-reducing agents
- All PIs are CYP450 inhibitors (usually 3A4), CYP3A4 substrates, and substrates of P-glycoprotein

Li EH et al. Ann Pharmacother 2014; 48:998-1010

25

Examples of Major Protease Inhibitor Drug Interactions Due to CYP 450

Interacting Drug	Description of Interaction
Simvastatin	Contraindicated due to increase in simvastatin concentrations and toxicity
Midazolam	Contraindicated; increase in midazolam concentrations
Fluticasone (Inhaled)	Increase in fluticasone concentrations; case reports of Cushingoid symptoms. Use alternative therapy (beclomethasone)
Rifampin	Can decrease PI concentrations by >75%. Additional ritonavir or cobicistat does not overcome interaction. Consider rifabutin
Amiodarone	Contraindicated with tipranavir due to increase in both amiodarone and PI. Use with caution with other PIs
St. Johns Wort	Contraindicated; Can decrease PI concentrations

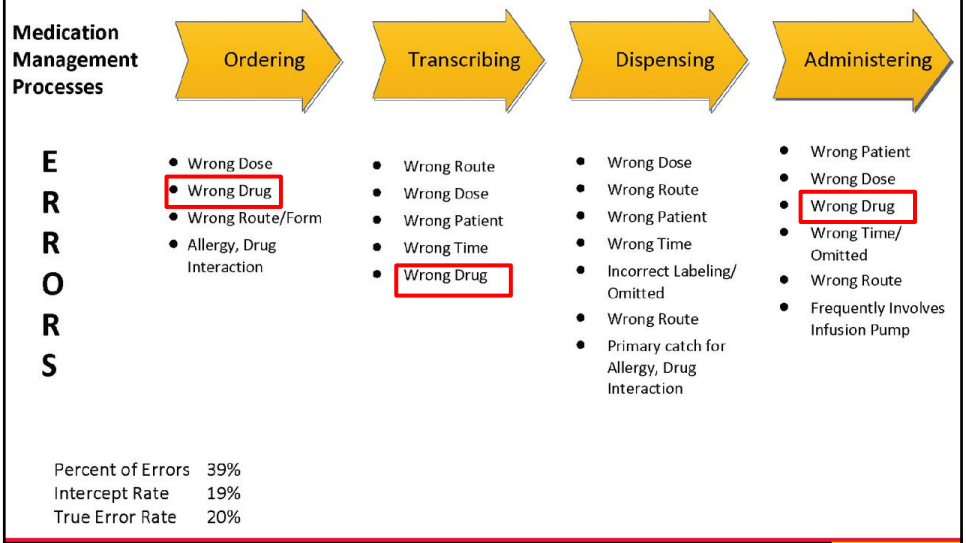
26

Examples of Other Common Drug Interactions

Antiretroviral	Interacting Drug	Description of Interaction
Integrase Inhibitors		
ALL	Products containing polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Cationic chelation; decreased absorption of INSTIs
Dolutegravir	Metformin	Inhibition of organic cation transporters in renal tubular cells; decreased clearance of metformin
NNRTIs		
Certain NNRTIs	Certain PIs	CYP3A4; increased/decreased concentrations of either agent
CCR5 Antagonist		
Maraviroc	Carbamazepine, Phenobarbital, Phenytoin	CYP3A4 induction, decrease in maraviroc. Use MVC 600 mg BID or an alternative antiepileptic agent.

27

Medication Errors – Types of Errors



Percent of Errors	39%
Intercept Rate	19%
True Error Rate	20%

Am J Health Syst Pharm. 2016 1;73(15):1144-65

28

Common Errors – Regimen Selection

- Traditionally, guidelines have recommended initiating and maintaining a combination antiretroviral regimen, including 3 active drugs.
  - Currently, 2-active drug regimens (i.e. Juluca) can be considered for virologically suppressed patients with no drug resistance
- Regimen selection errors are common in inpatients:
  - Systemic review: Proportion of regimen errors ranged from 3.7% to 69%.
  - Of 20 studies for which authors looked at regimen-related errors, the proportion of regimen errors at the time of prescribing made up more than one-third of the total errors in 8 studies.

Li EH et al. Ann Pharmacother 2014; 48:998-1010

29

Regimen selection Error Example – "Boosting"

- Ritonavir and cobicistat (newer) used as pharmacokinetic enhancers for PIs (and cobicistat for elvitegravir)
- Boosting of PI depends on the PI
  - Atazanavir (+/-), Fosamprenavir (+/-), Indinavir (+/-)
  - Nelfinavir- No
  - Darunavir, saquinavir, tipranavir MUST be boosted
- Errors occur when boosters are given alone, not given with an agent requiring boosting, or given with an agent not requiring boosting (e.g. co-formulated tablets of lopinavir/ritonavir or darunavir/cobicistat)

30

Regimen Selection Error Example – New Formulations

- Tenofovir available as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) (2015)

Tenofovir disoproxil fumarate (TDF) product	Tenofovir alafenamide (TAF) product
Tenofovir disoproxil fumarate (Viread) • Dose adjustments for HD	Tenofovir alafenamide (Vemlidy) • Not recommended CrCl <15 mL/min
TDF/emtricitabine (Truvada) • Not recommended CrCl <30 ml/min	TAF/emtricitabine (Descovy) • Not recommended CrCl <30 ml/min
TDF/emtricitabine/rilpivirine (Complera) • Not recommended CrCl <50 ml/min	TAF/emtricitabine/rilpivirine (Odefsey) • Not recommended CrCl <30 ml/min
TDF/emtricitabine/elvitegravir/cobicistat (Stribild) • Not recommended CrCl <50-70	TAF/emtricitabine/elvitegravir/cobicistat (Genvoya) • Not recommended CrCl <30 ml/min

31

Common Errors - Regimen Selection

Medication errors identified	Frequency	Percentage
Antiretroviral therapy (ART) ineligible client commencing ART	131	3.4
Incorrect dose (Low dose or high dose) prescribed	307	7.9
Incorrect antiretroviral drugs combinations/regimens prescribed	1028	26.4
No drug for the medical problem	318	8.2
No valid indication for the drug	229	5.9
Possible drug-drug interaction or contraindication present	772	19.8
Prescription order with incomplete prescriber/client details	463	11.9
Duration and/or frequency of medication inappropriate	647	16.6
Total	**3895**	**100.0**

Agu KA, et al. PLoS ONE 2014;9:e87338.

32

Medication Errors: Contributing Factors

Patient

- Renal or hepatic dysfunction
- Comorbidities
- Polypharmacy
- Impaired cognition
- Nonadherence
- Socioeconomic barriers

Drug

- Interactions
- Product formulation
- Drug name and labeling
- Drug abbreviations

Provider

- Lack of knowledge and expertise

Healthcare Setting

- High patient numbers
- Workload stresses
- Interruptions
- Distractions
- Communication barriers

Adapted from: Daniels LM, et al. JCOM 2016. 23(1):13-21

33

Patient

- Renal or hepatic dysfunction
  - One of the most common causes of medication prescribing errors
- Comorbidities
- Polypharmacy
- Impaired cognition
- Nonadherence
- Socioeconomic barriers

Lesar TS, et al. JAMA. 1997. 22-29;277(4):312-7.

34

Drug

- Interactions
- Product formulation
  - Co-formulated tablets
  - Tenofovir formulations
- Drug name and labeling
  - Brands/generics
  - Sound alike/look alike: contributed to 19% of errors in a 48-month evaluation period
    - Lamivudine/lamotrigine
    - Viramune/Viread/Viracept
    - Ritonavir/Retrovir
- Drug abbreviations

35

Drug - Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DRV	darunavir

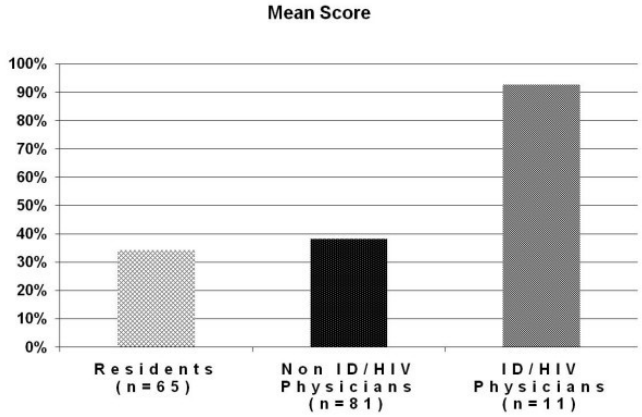
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IDV	indinavir
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir

NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	Zidovudine

36

Provider

- Lack of HIV-specific knowledge and expertise

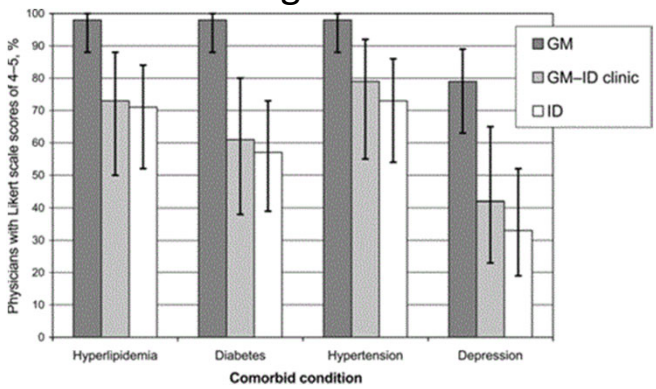


Arshad S, et al. J Int AIDS Soc 2009; 12:1.

37

Provider

- Relative discomfort with general medicine comorbidities among HIV Providers



Fultz SL, et al. Clin Infect Dis. 2005. 1;41(5):738-43.

38

Healthcare Setting

- High patient numbers
- Workload stresses
- Interruptions
- Distractions
- Communication barriers
  - Especially in heavily treatment-experienced patients

Agu KA, et al. PLoS ONE 2014;9:e87338.

39

Healthcare Settings – Communication Barriers

Table 1. Antiretroviral Errors Identified in the Initial Inpatient Drug Regimen

Type of Error	Number of Errors[a] All (N = 82)	Class 1 (n = 18)	Class 2 (n = 24)	Class 3 (n = 40)
Inpatient prescribing attributable errors	37	0	17	20
physician entered incorrect dose or frequency	14		6	8
physician entered incorrect drug	9		5	4
physician made an incomplete entry	6		3	3
drug from outpatient care not prescribed	8		3	5
Inpatient dispensing attributable errors	27	17	4	6
pharmacist entered incorrect dose	1			1
pharmacist entered incorrect frequency/administration time	12	12		
pharmacist entered incorrect drug	13	4	4	5
pharmacist made an incomplete entry	1	1		
ID/HIV clinic attributable errors	18	1	3	14
inappropriate drug continued due to inaccurate outpatient clinic documentation	2		1	1
inappropriate drug continued from outpatient HIV care	16	1	2	13

ID = infectious diseases.
[a]Class 1 errors were unlikely to cause patient discomfort or clinical deterioration. Class 2 errors had the potential to cause moderate discomfort or clinical deterioration. Class 3 errors had the potential to cause severe discomfort or clinical deterioration.

Pastakia SD, et al. Ann Pharmacother. 2008 Apr;42(4):491-7.

40

Consequences of ART errors

- Emergence of Drug Resistance
- Treatment Failure
  - Increased risk of transmission
- Drug Toxicities
- Loss of Patient Trust
- Legal Consequences
- Increased Costs

Daniels LM, et al. JCOM 2016. 23(1):13-21

41

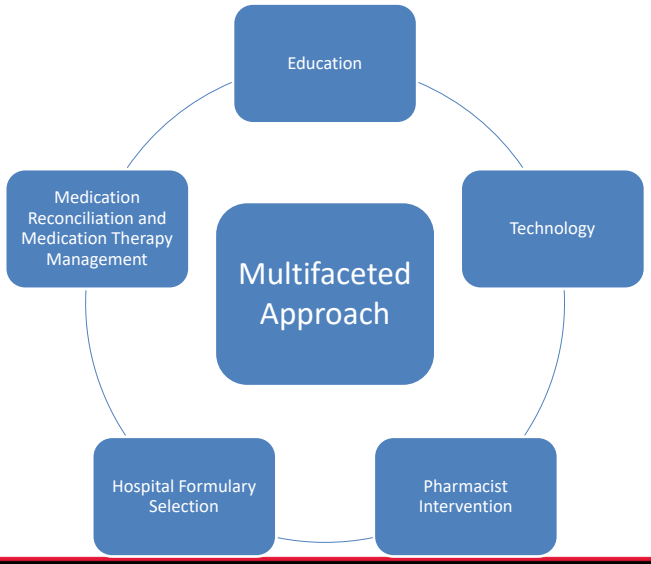
Consequences of ART Errors - Cost

- Healthcare costs avoided by preventing ART errors through pharmacist intervention amounted to $24,273/year for inpatient costs and $124 080/year for outpatient costs at a single US institution.

Merchen BA, et al. Abstracts of the Fifty-first Interscience Conference on Antimicrobial Agents and Chemotherapy Washington, DC, USA American Society for Microbiology Chicago, IL, 2011.

42

Interventions



Daniels LM, et al. JCOM 2016. 23(1):13-21

43

Intervention - Education

- Provider
  - Frequent, brief updates on new recommendations
  - Interventions targeting specific medication errors are transiently effective and may lack sustained efforts
- Patient
  - Encouragement of use of one pharmacy
  - Maintenance of one current medication list
  - Visual aids

Daniels LM, et al. JCOM 2016. 23(1):13-21

44

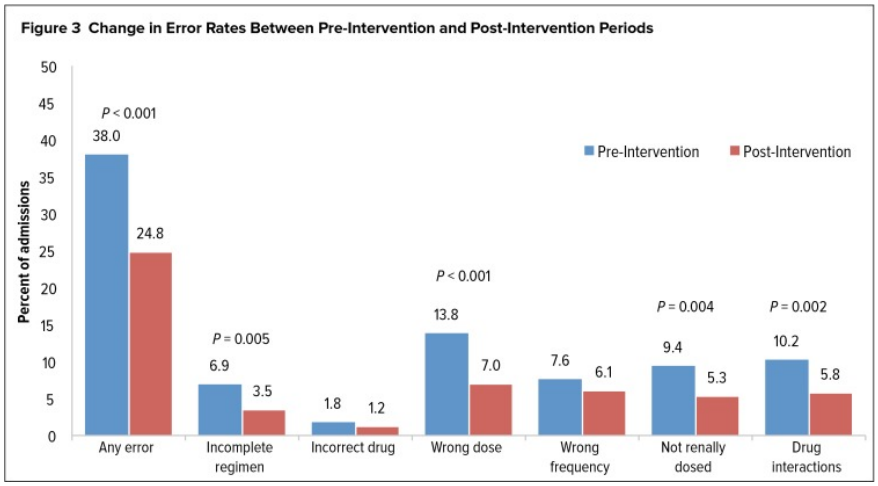
Intervention - Technology

- Barcoding systems
- Clinical decision support systems
- Computerized prescriber order-entry system (CPOE)

Daniels LM, et al. JCOM 2016. 23(1):13-21

45

Impact of Customized Order Entry Sets



Guo Y, et al. P T. 2015 May;40(5):353-60

46

CPOE

- Reduced confusion due to:
  - Abbreviations
  - Illegible writing
  - Like-alike/sound-alike drugs

- Can become quickly outdated
- System limitations
- "Alert fatigue"

Daniels LM, et al. JCOM 2016. 23(1):13-21

47

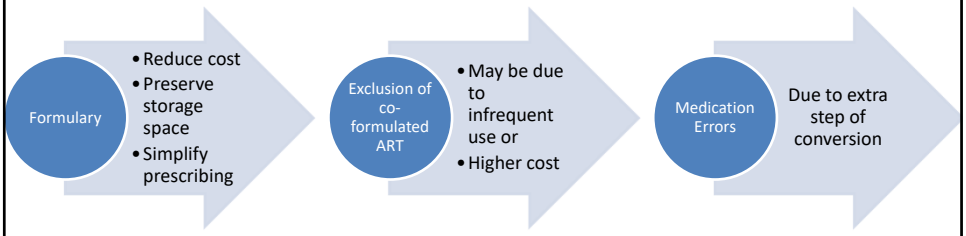
Intervention - Pharmacist

- Multiple studies have shown clinical pharmacists can help decrease ART medication errors
  - Most often correction > prevention
  - Daily review and follow-up is important
- Majority by pharmacists with specialized training in HIV
  - In one study utilizing pharmacists without specialized training in HIV, 54.7% of errors were never recognized or corrected

Commers T, et al. J Antimicrob Chemother 2014;69:262-7.

48

Intervention – Formulary Selections



Daniels LM, et al. JCOM 2016. 23(1):13-21

49

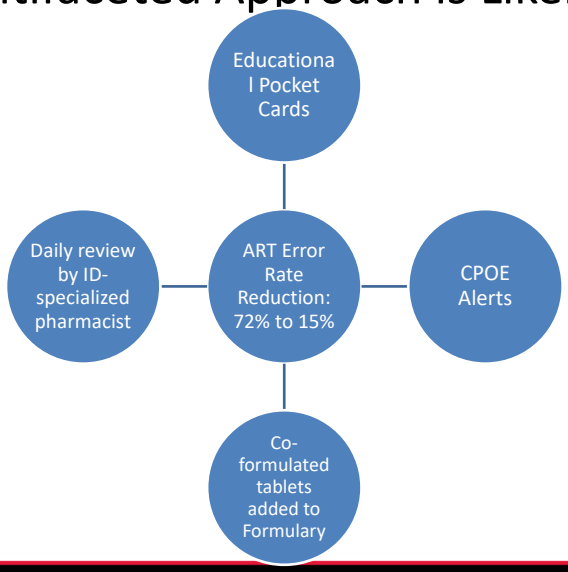
Intervention – Medication Reconciliation and Medication Therapy Management

- Medication Reconciliation is essential during transitions of care
  - Risk of error present on admission, throughout hospitalization, and upon discharge
- Outpatient medication therapy management via a pharmacist or multi-disciplinary team have been shown to result in lower hospital re-admission rates

Cavanaugh JJ, et al. J Manag Care Spec Pharm 2015;21:256-60.
Bellone JM, et al. J am Pharm Assoc 2012; 52:358-62

50

A Multifaceted Approach is Likely Best



Daniels LM, et al. Am J Health Syst Pharm 2012; 69:422-30

51

HIV-Specific Resources

- US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.
  - http://www.aidsinfo.nih.gov/
- University of Liverpool
  - http://www.hiv-druginteractions.org

52

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Self-Assessment Questions

53

Question 1

- Which of the following is NOT a common antiretroviral medication error?
  - A) Administering inhaled fluticasone with atazanavir
  - B) Ordering Stribild instead of Genvoya in a patient with a creatinine clearance of 40 ml/min
  - C) Not dose-adjusting abacavir in a patient on iHD
  - D) Prescribing darunavir without ritonavir

54

Patient Case

SF is 54 year old female with HIV (VL 124K, CD4 150, heavily treatment-experienced) presenting for CP, admitted to the inpatient cardiology service. Her PMH includes HLD, HTN, and history of MI. She states she is not sure of her HIV regimen and has not been taking any of her medications. According to her last outpatient clinic note, she is as on (an incomplete) regimen of darunavir + ritonavir + Viread. The team orders Prezcobix + ritonavir + Viramune.

55

Question 2

- Which of the following factors did NOT contribute to the inappropriate regimen the inpatient team ordered?

A) Patient – nonadherence
B) Drug – drug interactions
C) Provider – lack of HIV-specific knowledge and expertise
D) Drug – drug name and labeling
E) Healthcare setting – communication barriers

56

Question 3

- Which of the following is a possible outcome due to the regimen prescribed in SF's case?

A) Virologic suppression

B) Drug toxicities

C) Decreased cost to SF due to a cheaper regimen

D) Decreased risk of HIV transmission

E) A and D

57

Question 4

- How could the errors in the SF's case have best been prevented?

A) A single educational session to the providers aimed at reducing medication errors

B) CPOE with pre-populated ART drug regimens

C) Single review of ART regimen at admission by an ID trained pharmacist

D) Educational pocket cards for providers plus daily review of the SF's regimen by an ID-trained pharmacist

E) Formulary addition of more ART combination tablets

58

Summary

- Errors related to ART are common
  - Most often due to mistakes with regards to dosage, drug interactions, and regimen selection
- Factors contributing to ART errors include those related to the patient, medications, provider, and healthcare setting
- Consequences of ART errors include emergence of drug resistance, treatment failure, drug toxicities, loss of patient trust, legal consequences, and increased costs
- Interventions to reduce ART medication errors should ideally employ a multifaceted approach

59

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Antiretrovirals: Medication Errors and Medication Safety

Mary Banoub, PharmD

60

Psychiatric Aspects of HIV Care

Assessing and Addressing a Wide Range of Problems

1

Charles Robinson, M.D.

- Assistant Professor of Psychiatry, University of Maryland, Baltimore
- Director of Mental Health Services at the Evelyn Jordan Center of the IHV
- Working with people with HIV for 20 years

2

Disclosures

- I have no relevant financial disclosures; I will not be discussing off-label use of medications. This program is supported by funded research.

3

Three Categories of Problems

- 1. The persons pre-existing mental health liabilities
- 2. The person's reaction to HIV diagnosis, symptoms, and stigma
- 3. The impact of HIV disease on the brain

4

Sequential, Interacting Problems

- Patients with HIV Dementia, for example, will almost certainly have had pre-existing liabilities such as substance use disorders, trauma related disorders, or depression, and will also have experienced emotional reactions to diagnosis, symptoms, and others' attitudes. These are all likely to affect HIV care, adherence, and interactions with providers.

5

THE PERSON'S PRE-EXISTING LIABILITIES

- Substance Use Disorders
- Trauma and related disorders
- Major Depression
- Psychotic Disorders

6

SUBSTANCE USE DISORDERS

- Extremely prevalent, generally chronic and recurring.
- Lead to much provider-patient conflict, non-adherence, and additional medical comorbidities.
- When active, effectively preclude treatment of other mental health disorders—their drugs are stronger than our drugs.

7

Addressing SUD

- Useful to talk about SUD as a shared problem that prevents treatment of underlying problems that both you and your patient want to address.
- Propose a plan, let the patient have input, but—
- Don't begin treatment of depression, anxiety, or trauma-related disorders until after there has been substantial progress in reducing substance use.
- Agonist therapies, especially buprenorphine/naloxone are often helpful and necessary.

8

Drugs to Beware—

When you become your patient's dealer

- Opioids, stimulants, and benzodiazepines, of course and sedatives like Zolpidem
- Promethazine, clonidine, quetiapine (Seroquel®), pregabalin (Lyrica®), gabapentin—all potentiate opioids and can be used to get high
- Sedating, anticholinergic medications like diphenhydramine, amitriptyline, etc.
- More rarely, bupropion and venlafaxine

9

TRAUMA

- Again, **extremely** prevalent in the HIV-infected population.
- Frequently compounded and multiple, extending through childhood into adulthood.
- Frequent entrée into substance use disorders.

10

What is Trauma?

- Not just Posttraumatic Stress Disorder
- An event or combination of circumstances and events that adversely affects an individual beyond their ability to maintain or develop stable coping
  - Not just adversity or unpleasantness
  - Doesn't happen in a vacuum but in the context of a person's whole life
  - Can have a variety of outcomes

11

Types of Trauma

- Interpersonal vs. Impersonal
- Childhood vs. Adult
- Individual vs. Group
- Direct involvement vs. Witnessed
- Sexual vs. Physical vs. Psychological
- Single Incident vs. Sustained or Repeated
- Culturally sanctioned vs. Aberrant

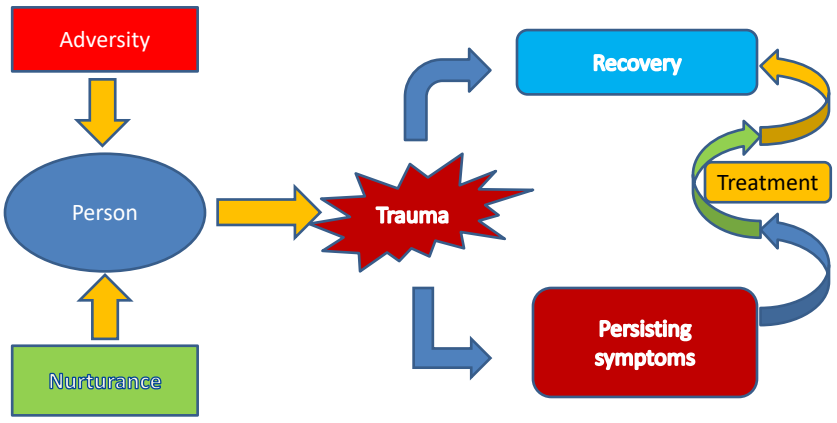
12

Factors that worsen or lessen the effects of trauma

Lessening	Exacerbating
Impersonal or Stranger perpetrator	Intimate or Caregiving perpetrator
Higher socioeconomic status	Poverty
High nurturance, low adversity before	Prior traumas
Emotionally supportive response after	Denial or blaming response
Supportive societal environment	Stigma
Temperamental resilience	Predisposition to anxiety, depression, dissociation, etc.

13

Life model of trauma



14

Trauma in the lives of People with HIV

- Markedly higher rates of childhood physical and sexual trauma than the general population (generally about or above 50%)
- Significantly higher rates of adult traumas (rape, physical assault, intimate partner violence)
- Includes traumas inflicted because of others' awareness of a person's HIV diagnosis.

15

Identifying Traumatic Events

- Difficult in many ways
  - Same events not necessarily traumatic to different people or even to the same person in different circumstances
  - Traumatized individuals vary in their ability to identify, disclose, remember, and report events
  - Because of the multiple ways people may be traumatized, and the difficulty of screening for all those ways simultaneously, screening instruments can be lengthy or overly vague

16

Identifying Trauma by its Effects

- Also difficult because of the variety of potential after-effects
  - Acute Stress Disorder/PTSD
  - Other Anxiety Disorders
  - Depression
  - Dissociation
  - Substance Use Disorders
  - Personality Disorders (Maladaptive Coping Styles)

17

General Types of ASD/PTSD Symptoms

- Intrusions (nightmares, flashbacks, memories)
- Avoidance (of thoughts and external reminders)
- Negative changes in cognitions (amnesia, distorted thinking) and mood (shame, emotional disconnection, etc.)
- Increased arousal and reactivity (irritability, aggression, recklessness, startle, etc.)

18

Primary Care PTSD Screen (PC-PTSD)

- In your life, have you ever had any experience that was so frightening, horrible, or upsetting that in the past month you
- 1. Have had nightmares about it or thought about it when you did not want to?
- 2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
- 3. Were constantly on guard, watchful, or easily startled?
- 4. Felt numb or detached from others, activities, or your surroundings?

19

Primary Care PTSD Screen (PC-PTSD)

- Three or more "yes" answers is a positive screen for PTSD.
  - This is a screen for current PTSD, not past, and not for any other disorder arising from trauma.
  - This is a screen, not a definite diagnosis.
  - Very possible to have false negatives, especially in chronic PTSD related to developmental trauma.
- This and other instruments are available at VA website, https://www.ptsd.va.gov/professional/assessment/all_measures.asp

20

Psychotherapy for Trauma-related Disorders

- Cognitive-Behavioral Therapy and variations on it have overall the best support
  - Basics of CBT
    - Thoughts, behaviors, and actions all affect each other
    - Behavioral change, thought identification and regulation, and increased identification and awareness of emotions in context of behaviors and thoughts
  - Coordinated group and individual treatment generally favored but widely applicable research is lacking, and treatment model variations are innumerable

21

Pharmacologic treatment of trauma disorders

- Antidepressants, especially SSRI's (escitalopram, fluoxetine, etc.) and SNRI's (venlafaxine, duloxetine, etc.) are the mainstay
- Prazosin for nightmares
- Multiple rather than single medications are the rule, and essentially every medication ever used for a psychiatric condition has been reported to be helpful at some point
  - Antipsychotics
  - Mood stabilizers

22

Depression

- Many screening instruments available, PHQ-9 is a reasonable choice
- First-line choices for antidepressants
  - Citalopram, start at 10 mg/day with food, increase to 20 mg/day with food after a week as tolerated.
  - Escitalopram, start at 5 mg/day with food, increase to 10 mg/day with food after a week as tolerated
  - Bupropion XR, start at 150 mg/day, with food, increase to 300 mg/day after a month if insufficiently effective
  - Mirtazapine, start at 15 mg at bedtime, increase to 30 mg at bedtime after a week
- Psychotherapy is also recommended

23

Major Mental Illness

- Schizophrenia, Bipolar I Disorder, and Major Depression with Psychotic Features
- Learn to recognize and refer.
  - Do not attempt to initiate treatment as a primary provider, though continuation of established care may be OK.
  - Send floridly symptomatic people to the Emergency Room. Do not attempt to establish a reasonable treatment plan with a grossly psychotic person.

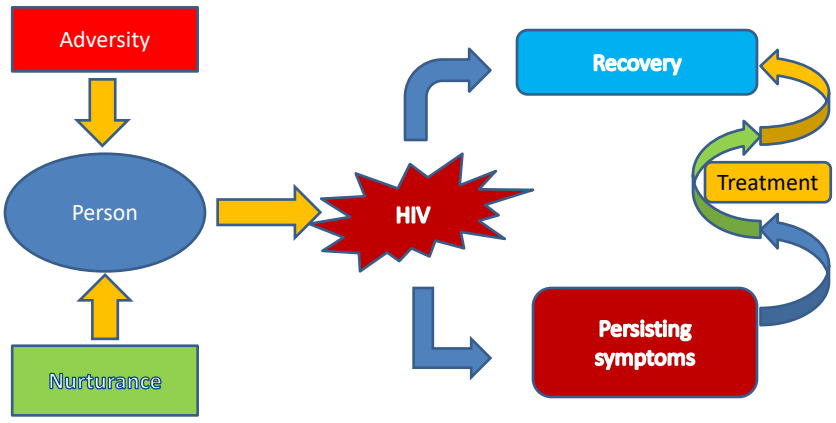
24

THE PERSON'S REACTION TO HIV DIAGNOSIS, SYMPTOMS, AND STIGMA

- Very sensitive to the person's support system, his/her previous experience with others who have had HIV, his/her idea of what HIV is like or how long he/she can expect to live.
- Affect access to care--people may avoid rather than seek treatment, particularly if they or a friend has had an unpleasant experience with health care.
- May include any of Kubler-Ross's stages (anger, bargaining, denial, despair, acceptance), which can fluctuate rapidly in the presence of a provider. The discovery of Kaposi's Sarcoma in the mouth, for instance, may provoke a rapid succession of these stages as the person tries to adapt to the discovery and contain themselves within the clinical situation.

25

Life model of HIV



26

Trauma and HIV

- HIV can be a trauma
  - Diagnosis
  - Onset of symptoms
  - Traumatic medical and treatment events
- Context can worsen or lessen that trauma
  - Stigma
  - Violence
  - Loss
    - Elements of both individual and shared trauma
    - Directly experienced and witnessed

27

Trauma and HIV

- Even when HIV Diagnosis is not itself a trauma, there is broad overlap between common emotional reactions and thoughts associated with the diagnosis and the phenomena of trauma.
- In people with histories of trauma, old behavioral and emotional patterns are likely to be triggered.

28

MENTAL DISORDERS CAUSED BY HIV

- HIV Dementia is the classic
  - Slowing of cognition and often movement
  - NOT detectable using Mini-Mental, use HIV Dementia Scale, Mental Alternations Test
  - Can have onset with mania or, more frequently, depression
  - Many psychiatric medications are useful for symptoms, but antiretrovirals are the only treatment
- Minor cognitive disorders are more common

29

Other HIV-related brain diseases

- CMV, Toxoplasmosis, Cryptococcal meningitis, vasculitis, PML, and a host of poorly-characterized late-stage syndromes
- May compound HIV Dementia
- Treatment is for the underlying cause, and symptomatic treatment with psychiatric meds may be useful as well.

30

Take-Home Messages

- There are three general categories of psychiatric phenomena related to HIV: pre-existing, psychological response to disease, and direct effect of HIV and OI's on the CNS.
- Substance Use Disorders are common and when active prevent successful treatment of underlying psychiatric disorders.
- Trauma-related disorders and depression are so common that they must be addressed in primary HIV care, and there are basic, sound steps to take.
- Major mental illnesses require specialist input and, if very symptomatic, emergency room intervention.
- Many non-scheduled medications are abused, particularly in combination with narcotics, and they should be prescribed very cautiously.
- Teamwork and collaboration—and avoidance of things that make problems worse—are key.

31

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32

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