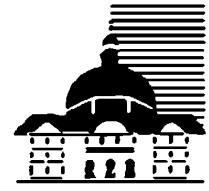
“Wonder pills”, breakthroughs and continuing challenges : HIV antiviral treatment revisited

Dr Valérie POURCHER-MARTINEZ
Associate Professor
Hôpital Pitié-Salpêtrière
Infectious Diseases Department
Paris, France



Conflicts of interests

- Giléad
- ViiV Healthcare
- BMS
- MSD
- Janssen

Question 1

- Do you want to treat an HIV infected patient with 1 000 CD4 cell count ?

- YES

- NO

Question 2

- Can you be used integrase inhibitors for HIV naive adults?

- YES

- NO

Question 3

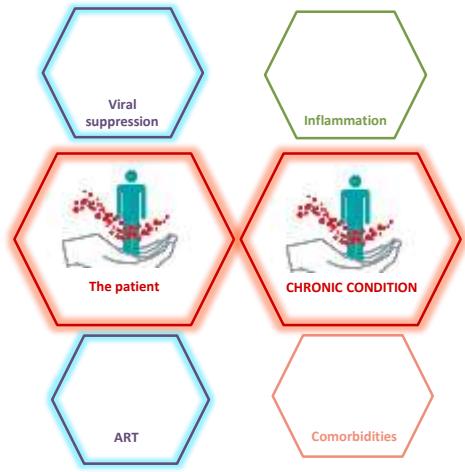
- Could you be used antiretroviral drugs to prevent HIV infection for high risk acquisition subjects ?
- YES
- NO

37 millions of HIV-infected patients

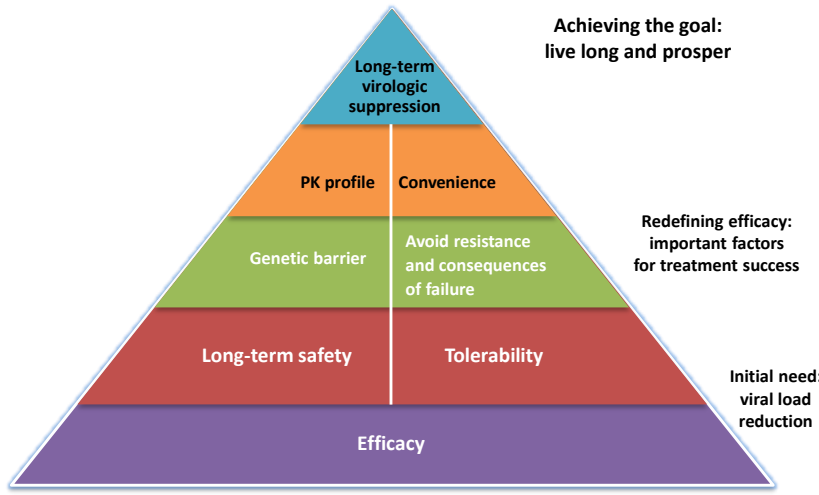
HIV in 2016 ?

Current situation

- Innovations in therapy have transformed HIV into a chronic condition; long-term health is becoming more important as HIV-positive patients are living longer

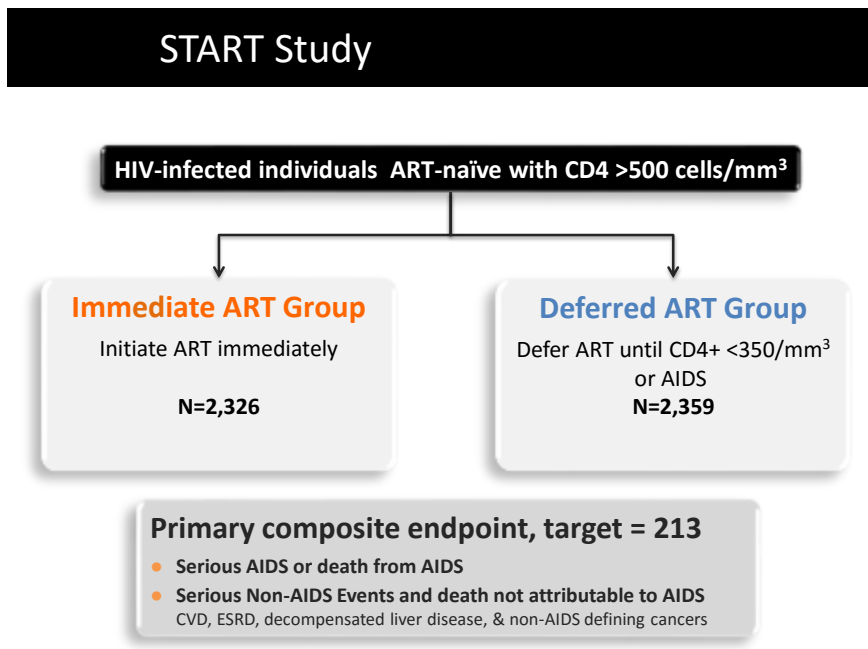


What do physicians want from treatment?



PK, pharmacokinetic.
Graeme Moyle, personal communication

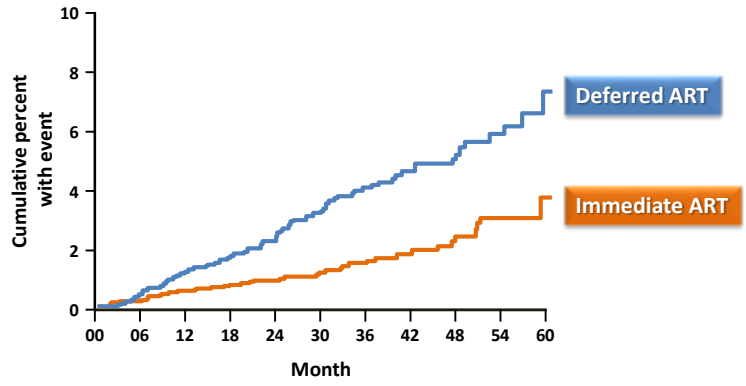
When to start ART ?



INSIGHT START Study Group. *N Engl J Med.* 2015

57% reduced risk of serious events or death with immediate ART

- 4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30–0.62; $p<0.001$)



INSIGHT START Study Group. *N Engl J Med.* 2015; Lundgren J, *et al.* IAS 2015

International Guidelines 2015
A major step towards universal access to ART

Guideline	AIDS or HIV-Related Symptoms	CD4+ <350/mm³	CD4+ >350-500/mm³	CD4+> 500 /mm³
DHHS-USA, 2013	Yes	Yes	Yes	Yes
International AIDS Society-USA, 2013	Yes	Yes	Yes	Yes
France, 2013	Yes	Yes	Yes	Yes
European AIDS Clinical Society, 2015	Yes	Yes	Yes	Yes
World Health Organization, 2015	Yes	Yes	Yes	YES

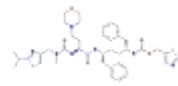
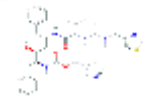
Gold standart: UNIVERSAL Treatment

Antiretroviral Therapy Goals

- Maximal control of viral replication below level of detection
- Immune restoration with CD4 > 500/mm^3
- Get a maximum of HIV infected patients in care with ART

Antiretroviral drugs available

Initial treatment choice: which booster?

Variable	Cobicistat	Ritonavir
Chemical structure[1,2]		
Enzyme inhibition[3]	CYP3A4; CYP2D6 (weak); P-gp	CYP3A4; CYP2C8; CYP2C9; CYP2D6; P-gp
Intrinsic anti-HIV activity[3]	No	Yes
eGFR (W144)[4]	−15.1 mL/min/1.73 m^2	−7.5 mL/min/1.73 m^2
GI tolerability (W144)[4]	Diarrhoea, 19.2% Nausea, 22.4%	Diarrhoea, 19.0% Nausea, 27.6%

CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; NCBI, National Centre for Biotechnology Information; P-gp, P-glycoprotein; UGT, uridine 5′-diphosphoglucuronosyltransferase.

1. Figure adapted from NCBI PubChem Substance Database SID=135626633. Available from: http://goo.gl/GI96z3. 2. Figure adapted from NCBI PubChem Compound Database CID=392622. Available from http://goo.gl/D4daqu. 3. Capetti et al. Expert Opin Pharmacother 2014 15:1289–98. 4. Gallant et al. J Acquir Immune Defic Syndr 2015;69:338–40. URLs accessed October 2015

Antiretroviral drugs : 2016

NRTI	NNRTI	Protease Inhibitors	Integrase Inhibitors	CCR5 Inhibitors
TDF TDF/FTC ABC ABC/3TC TAF soon	Nevirapine Efavirenz Rilpivirine Etravirine	Atazanavir Darunavir	Raltegravir Elvitegravir Dolutegravir	Maraviroc

Single Tablet Regimen (STR)

- **EFV/FTC/TDF (ATRIPLA®)**
- **RPV/FTC/TDF (EVIPLERA®)**
- **EVG/C/FTC/TDF (STRIBILD®)**
- **DTG/3TC/ABC (TRIUMEQ®)**
- TAF/FTC/EVG/C (Genvoya®)

EFV= efavirenz, FTC=emtricitabine, TDF=tenofovir Disoproxil Fumarate, RPV= rilpivirine, EVG/C= elvitegravir/cobicistat, DTG= dolutegravir, 3TC=lamivudine, ABC= abacavir

What do the latest guidelines say?

Treatment of naive patients

Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)[*,**]

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG[A, II]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[III, IV] + DTG	TDF/FTC 300[HIV]/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TDF/FTC/EVG/c[II, IV, VI]	TDF/FTC/EVG/c 300[HIV]/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[III, IV] + RAL	TDF/FTC 300[HIV]/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
2 NRTIs + NNRTI			
TDF/FTC/RPV[III]	TDF/FTC/RPV 300[HIV]/200/25 mg, 1 tablet qd	With food (min 390 Kcal required)	Only if CD4 count >200 cells/µL and HIV VL <100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r			
TDF/FTC[III, IV] + DRV/r	TDF/FTC 300[HIV]/200 mg, 1 tablet qd + DRV 600 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.

EACS guidelines 2015, version 8.0. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.

What do the latest guidelines say?

EACS 2015[1]*

"Recommended regimens (one of the following to be selected):

- **2 NRTIs + INSTI**
  - ABC/3TC/DTG
  - TDF/FTC + DTG
  - TDF/FTC/EVG/c
  - TDF/FTC + RAL
- **2 NRTIs + NNRTI**
  - TDF/FTC/RVP*
- **2 NRTIs + PI/r**
  - TDF/FTC + DRV/r

"

DHHS 2015[2]*

"There are now **five** recommended regimens for ART-naive patients: four INSTI-based regimens and one PI/r-based regimen, as listed below

- **INSTI-based regimens**
  - DTG/ABC/3TC – **only** for patients who are HLA-B*570 negative (A1)
  - DTG + TDF/FTC (A1)
  - EVG/c/TDF/FTC – **only** for patients with pre-ART CrCl > 70 mL/min (A1)
  - RAL + TDF/FTC (A1)
- **PI-based regimen**
  - DRV/r + TDF/FTC (A1)

"

*Consult guidelines for full recommendations and drug-specific information.
†Coformulated.
ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; BD, twice daily; c, cobicistat; DHHS, Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QD, once daily; r, ritonavir; RAL, raltegravir; RPV, rilpiravine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

1. EACS guidelines 2015, version 8.0. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
2. DHHS guidelines 2015. Available from: https://aidsinfo.nih.gov/guidelines. Accessed October 2015.

Treatment of naive patients

B) Alternative regimens (to be used when none of the preferred regimens are feasible or available, whatever the reason)

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC[I, II] + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before)
2 NRTIs + NNRTI			
ABC/3TC[I, II] + EFV [VII]	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd	At bed time or 2 hours before dinner	
TDF/FTC/EFV[III, IV]	TDF/FTC/EFV 300[VII]/200/600 mg, 1 tablet qd	At bed time or 2 hours before dinner	
2 NRTIs + PI/r or PI/c			
ABC/3TC[I, II] + ATV/r	ABC/3TC 600/300 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Co-administration with PPI is contraindicated.[VIII]
TDF/FTC[III, IV] + ATV/r	TDF/FTC 300[VII]/200 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	
ABC/3TC[I, II] + ATV/c	ABC/3TC 600/300 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	
TDF/FTC[III, IV] + ATV/c	TDF/FTC 300[VII]/200 mg, 1 tablet qd + ATV 300 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	Co-administration with PPI is contraindicated.[VIII] eGFR <70 mL/min: combination not recommended.
ABC/3TC[I, II] + DRV/r	ABC/3TC 600/300 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	Monitor in persons with a known sulfonamide allergy.
ABC/3TC[I, II] + DRV/c	ABC/3TC 600/300 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	
TDF/FTC[III, IV] + DRV/c	TDF/FTC 300[VII]/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + COBI 150 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy. eGFR <70 mL/min: combination not recommended.
TDF/FTC[III, IV] + LPV/r	TDF/FTC 300[VII]/200 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	Use with caution in persons with high cardiovascular risk
Other combinations			
3TC[II] + LPV/r	3TC 300 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	
RAL[III] + DRV/r	RAL 400 mg, 1 tablet bid +DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. Co-administration of antacids containing Al or Mg not recommended.

Experienced patients

- Choice depend of the reasons of the switch
  - Simplification
  - Adverse effects
  - DDI
  - virologic failure

- Before to switch, we need to check
  - resistance genotype
  - pharmacokinetic parameters of antiretroviral drugs used
  - potential DDI

Specific population

Adverse effects

Adverse Effects of ARVs & Drug Classes

Bold: Frequent effects
Red: Severe effects
Black: Neither Frequent nor Severe[ii]

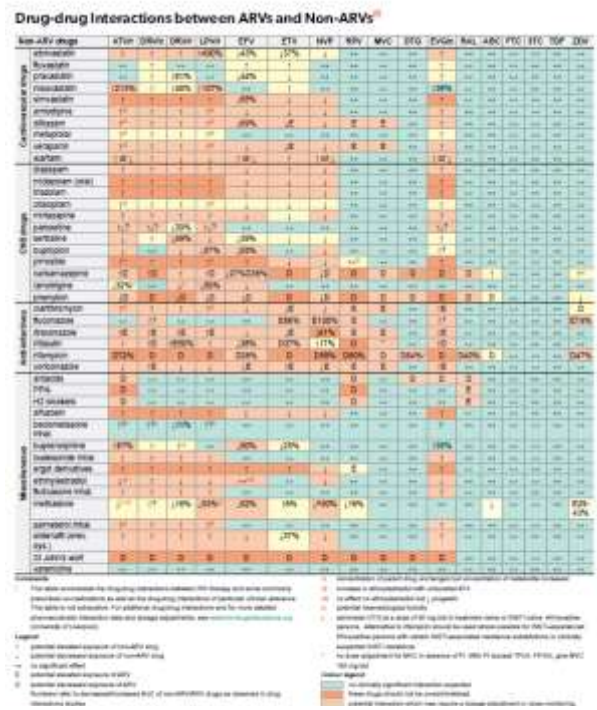
	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTIs										
ABC	Rash*	Nausea* Diarrhoea*		IHD						*Systemic hyper-sensitivity syndrome (HLA B*5701 dependent)
ZDV	Nail pigmen-tation	Nausea	Steatosis		Myopathy, Rhabdo-myolysis			**Lipoatrophy**	Dysilpi-daemia, Hyperlacta-taemia	Anaemia
d4T		Pancreatitis	**Steatosis**				**Peripheral neuropathy**		**Dysilpi-daemia,** Hyperlacta-taemia	
ddI			Steatosis, Liver fibrosis	IHD					Hyperlacta-taemia	
3TC										
FTC										
TDF[iii]					↓ BMD, Osteomalacia ↑ Fractures risk	↓ eGFR, Fanconi syndrome				
NNRTIs										
EFV	Rash		Hepatitis				**Depression, Sleep disturbanc-es, Headache,** Suicidal ideation		**Dysilpi-daemia,** Gynaeco-mastia	**↓ plasma 25(OH) vitamin D,** Teratogen-esis
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersen-sitivity (CD4 count-and gender-de-pendent)
RPV	Rash		Hepatitis			↓ eGFR[iv]	Depression, Sleep disturbances, Headache			

PIs										
ATV[v]		**Nausea and Diarrhoea**[ii]	**Hyperbiliru-binaemia,** Jaundice, Cholelithiasis			↓ eGFR, Nephrolith-iasis			Dysilpi-daemia	
DRV[v]	Rash					Nephrolith-iasis			Dysilpi-daemia	
FPV[vi]	Rash			IHD					**Dysilpi-daemia**	
IDV[vi]	**Dry skin,** Nail dystrophy		Jaundice	IHD		**Nephrolith-iasis**		**↑ Abdominal fat**	**Dysilpi-daemia,** Diabetes mellitus	
LPV				IHD		↓ eGFR			**Dysilpi-daemia**	
SQV[vi]									Dysilpi-daemia	
TPV[vi]			Hepatitis				Intracranial haemorrhage		Dysilpi-daemia	
Boosting										
RTV						↓ eGFR[iv]				
COBI						↓ eGFR[iv]				

FI										
ENF	Injection nodules									Hypersensi-tivity
INSTI										
RAL		Nausea			Myopathy, Rhabdomy-olysis		Mood changes			
DTG	Rash		Nausea			↓ eGFR[iv]	Headache			Systemic hyper-sensitivity syndrome (<1%)
EVG/c		**Nausea, Diarrhoea**	**Hyperbiliru-binemia**			↓ eGFR[iv]	Headache			
CCR5 inhibitor										
MVC			Hepatitis	IHD						↑ Infections risk

Drug-drug interactions

- Various
- Metabolic voice
- Use of enzymatic inhibitor/inductors



www.hiv-druginteractions.org

New drugs, new strategies and futur

- Same efficacy or more…

The need for novel drugs and novel classes

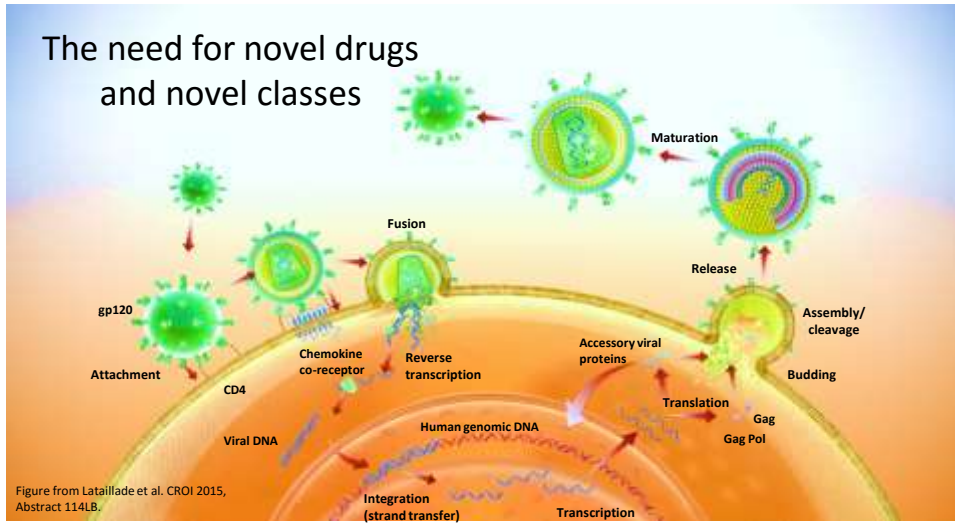


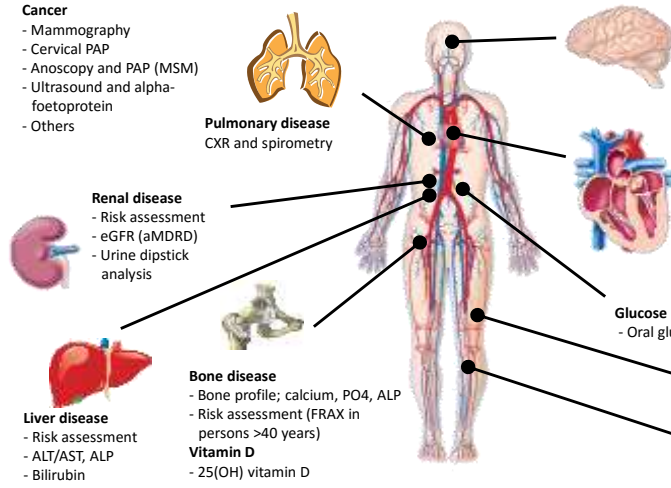
Figure from Lataillade et al. CROI 2015, Abstract 114LB.

New drugs targeting different stages of the HIV-1 life cycle are needed to[1,2]

- Provide options for treatment-experienced and -naive patients
- Reduce drug–drug interactions
- Improve tolerability and toxicity
- Provide novel formulations/ delivery systems
- Reduce pill burden

1. Dau et al. Drugs 2009;1:31–50. 2. Andrieux-Meyer et al. J Int AIDS Soc 2012;15:17986.

HIV infection and ART can have long-term effects on numerous aspects of health



Cancer
- Mammography
- Cervical PAP
- Anoscopy and PAP (MSM)
- Ultrasound and alpha-foetoprotein
- Others

Pulmonary disease
CXR and spirometry

Renal disease
- Risk assessment
- eGFR (aMDRD)
- Urine dipstick analysis

Liver disease
- Risk assessment
- ALT/AST, ALP
- Bilirubin

Bone disease
- Bone profile; calcium, PO4, ALP
- Risk assessment (FRAX in persons >40 years)

Vitamin D
- 25(OH) vitamin D

Neurocognitive impairment
- Screening questionnaire

Depression
- Questionnaire

Cardiovascular disease
- Risk assessment (Framingham score) in all men >40 and women >50 years without CVD
- ECG prior to ARVs in certain patients

Hypertension
- Blood pressure

Lipids
- TC, HDL-c, LDL-c and TG

Glucose
- Oral glucose tolerance test/HbA1c

Body composition
- BMI

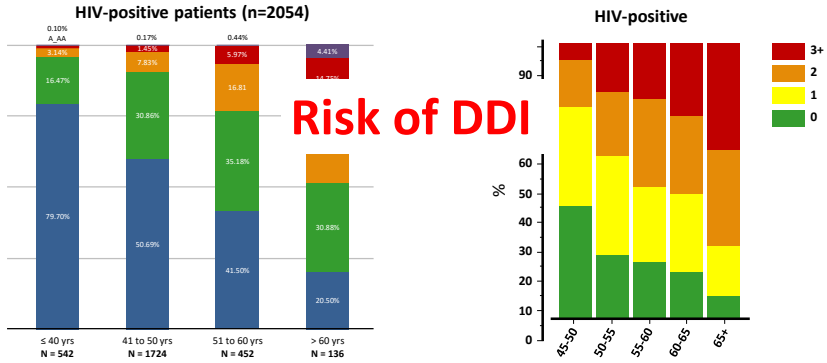
Haematology
- FBC
- Haemoglobinopathies
- G6PD

***See guidelines for detail on follow-up frequency, subgroups to be screened and further information**
HANA, HIV-associated non-AIDS

EACS guideline version 7.0, October 2013; [1] McArthur JC, et al. *Ann Neurol*. 2010;67:699-714; [2] Nguyen ML, et al. 18th IAC; Vienna; 2010. Abstract WEAB0105; [3] Freiberg MS, et al. *JAMA Intern Med*. 2013;173:614-622; [4] Brown TT, et al. *AIDS*. 2006;20:2165-2174; [5] Towner WJ, et al. *J Acquir Immune Defic Syndr*. 2012;60:321-327; [6] Lucas GM, et al. *Clin Infect Dis*. 2014;59:e96-e138.

High prevalence of multiple comorbidities in HIV-infected ageing cohorts

(Left) Case-control study involving ART-experienced HIV+ patients treated at Modena University from 2002 to 2009;[1]
(Right) Prospective comparative cohort of HIV+ patients in Amsterdam[2]



- The prevalence of polypathology for 51–60 years group was 20% in the Modena cohort while it was 35% in the AGEhIV cohort
- In both studies, polypathology prevalence was higher in cases for all ages

1. Guaraldi G. CID 2011;53:1120–1126; 2. Treatment Action Group. The Immune System, HIV & aging. April 2014. Available at: http://www.treatmentactiongroup.org/hiv/2013/immune-system-hiv-and-aging

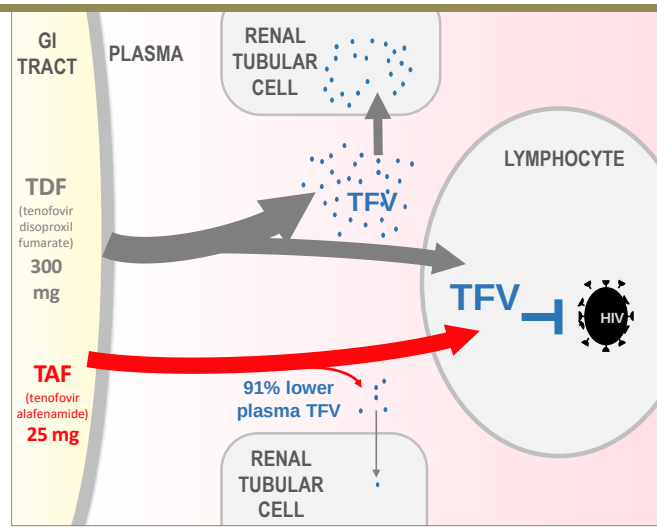
New drugs and futur

- TAF
- Cabotegravir
- Doravirine
- Maturation and inhibition attachment
- New strategies

Tenofovir Alafenamide in a Single-Tablet Regimen

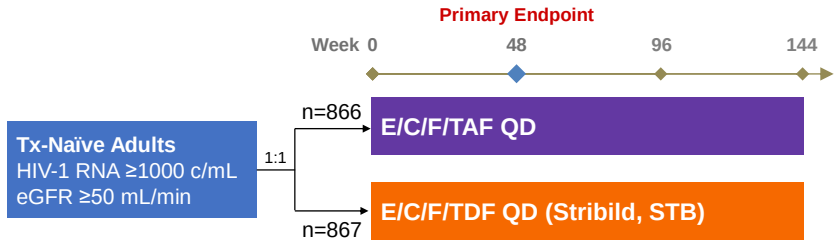
1. DeJesus E, et al. Lancet 2012;379:2429-38; 2. Gallant JE, et al. J Infect Dis 2013;208:32-9; 3. Sax PE, et al. Lancet 2012;379:2439-48; 4. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-55; 5. Sax PE, et al. J Acquir Immune Defic Syndr 2014;67:52-8.

Mechanism of Action: TAF vs TDF



1. Lee W et al. Antimicr Agents Chemo 2005;49:1898-906; 2. Birkus G, et al. Antimicr Agents Chemo 2007;51:543-50; 3. Babusis D, et al. M Pharm 2013;10:459-66; 4. Ruane P, et al. JAIDS 2013;63:449-5; 5. Sax P, et al. JAIDS 2014;67:52-8; 6. Sax P, et al. Lancet 2015;385:2606-15

Study Design: Studies 104 and 111



- Two Phase 3 randomized, double-blind, double-dummy, active-controlled studies
  - Study 104 (North America, EU, Asia), Study 111 (North America, EU, Latin America)
  - Stratified by HIV-1 RNA, CD4 cell count, geographic region
- Primary endpoint: proportion of patients with HIV-1 RNA <50 copies/mL (Taqman 2.0)
  - Non-inferiority (12% margin) based on Week 48 FDA snapshot analysis
  - Combined efficacy analysis pre-specified
  - Pre-specified Week 48 safety endpoints: serum creatinine, proteinuria, hip BMD, spine BMD

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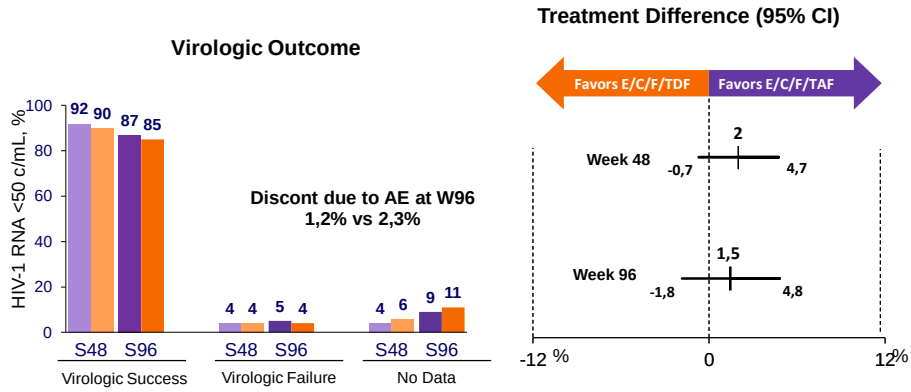
Week 48 and 96 Virologic Outcomes



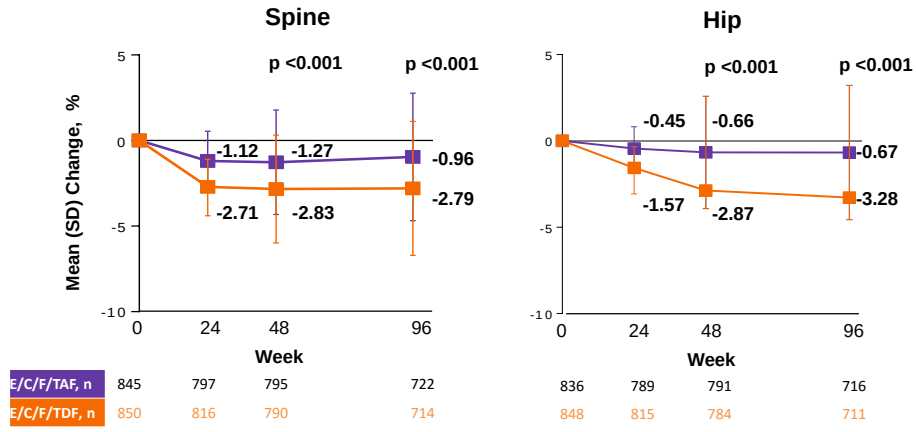
VF with resistance through week 96: 1% (10 of 866) on TAF vs. 1% (8 of 867) on TDF

- NRTI-R: M184V/I (9 TAF vs 6 TDF); K65R/N (2 TAF vs 3 TDF)
- INSTI-R: 8 TAF vs. 5 TDF, all genotypically susceptible to DTG

At Week 96, E/C/F/TAF was non-inferior in efficacy to E/C/F/TDF

Wohl D, et al. EACS 2015. Barcelona, Spain. Best Poster #LBBPD1/1

Changes (%) in Spine and Hip BMD Through Week 96



Less spine and hip BMD loss on E/C/F/TAF maintained through week 96 with no further BMD loss after week 48

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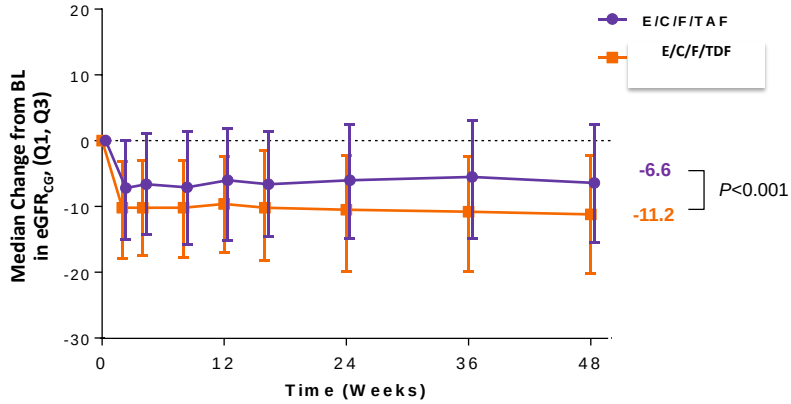
Wohl D, et al. EACS 2015. Barcelona, Spain. Best Poster #LBBPD1/1

Changes in eGFR (Cockcroft-Gault) Through Week 48

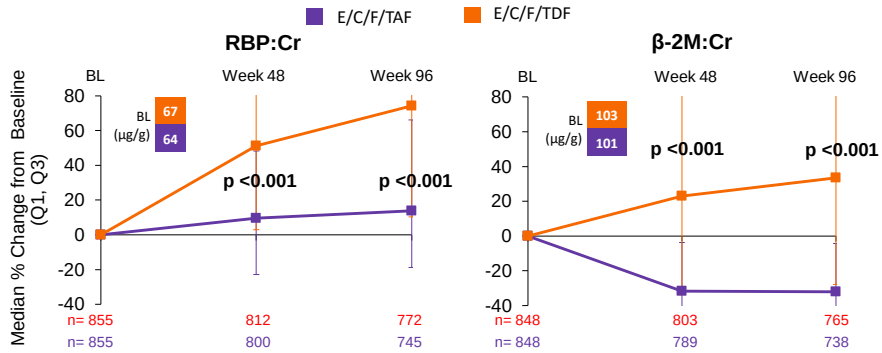


Less GFR decline with E/C/F/TAF compared to E/C/F/TDF (p<0.001)

Pattern of early decline (2 wks) then stable eGFR is consistent with cobicistat inhibition of tubular secretion of creatinine

Sax P, et al. CROI 2015. Seattle, WA. Oral #143LB

Changes (%) in Quantitative Tubular Proteinuria



On **E/C/F/TAF** through Week 96

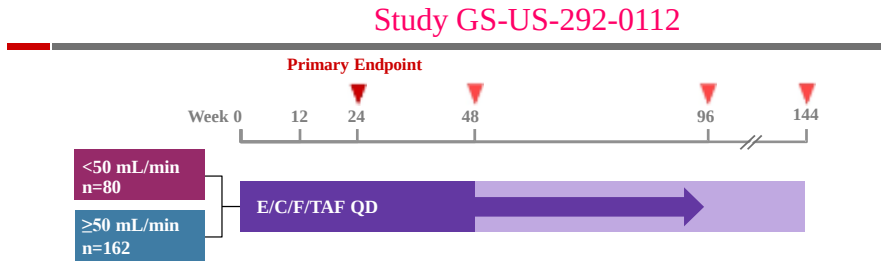
- Little to no impact on tubular function was maintained
- No Fanconi Syndrome, PRT, or subclinical tubulopathy

On **E/C/F/TDF** through Week 96

- 1 Fanconi Syndrome (discontinuation) & 1 subclinical tubulopathy

Wohl D, et al. EACS 2015. Barcelona, Spain. Best Poster #LBBPD1/1

Elvitegravir/Cobicistat/Emtricitabine/TAF in Participants With Glomerular Filtration Rate <50 mL/min: 96-weeks Results

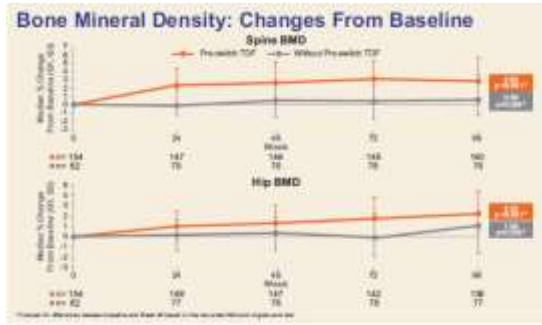


- Phase 3, 144-wk, multicenter, open-label study of virologically suppressed adults switching to E/C/F/TAF
- Eligibility: stable eGFRCG (30–69 mL/min)
- Primary endpoint: change from baseline in eGFR at Week 24
  - Actual GFR assessed by iohexol clearance and intensive PK performed in subset of participants between weeks 2 and 8

Post F, CROI, abstract 680, 2016

Change in eGFR From Baseline to Week 96

- 92% with HIV RNA < 50 c/ml at Week 96



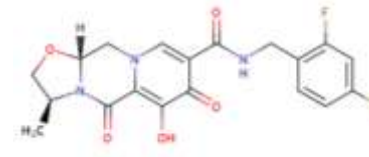
- No proximal renal tubulopathy or Fanconi syndrome

Change in Spine and Hip Bone Mineral Density

Post F, CROI, abstract 680, 2016

Cabotegravir

What is it?
New integrase inhibitor[1]



Administration?
Oral and long-acting injectable formulations[1,2]

Why are we interested?
Allows novel combination with RPV in a dual regimen; potential to overcome adherence challenges via monthly or quarterly (IM/SC) injections[1–3]

Current status?
96-week phase 2b data on oral combination published in 2015[4], bioavailability of phase 3 tablet completed in 2015[5]

Target population?
Treatment-naive (once suppressed after treatment with two NRTIs) patients for oral[4]
Switch for injectable[5]

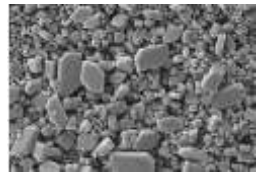
NRTI, nucleos(t)ide reverse transcriptase inhibitor; RPV, rilpivirine; SC, subcutaneous.
1. Trezza et al. Curr Opin HIV AIDS 2015;10:239–45. 2. Spreen et al. J Acquir Immune Defic Syndr 2014;67:487–92.
3. NCT02478463. Accessed October 2015. 4. Margolis et al. Lancet Infect Dis 2015;doi:10.1016/S1473-3099(15)00152-8. (Epub ahead of print).
5. NCT02345707. Accessed October 2015.

RPV LA: G001 formulation

- Sustained release, apparent terminal half-life 30–90 days
- Plasma RPV levels in range with those for oral RPV in Phase 3
- Substantial distribution into genital and rectal tract
- Generally safe and well tolerated in Phase 1
- Cold chain storage (2 – 8 ° C) - Or not?

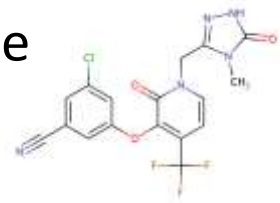
Target G001

'Aged' G001



- Storage room temperature
  - Impact on particle size
  - Impact in vitro dissolution profile
  - In vivo relevance unknown
- Phase 1 relative BA study to evaluate the in vivo impact

Doravirine



What is it?
Novel NNRTI[1]

Administration?
Daily tablet[1]

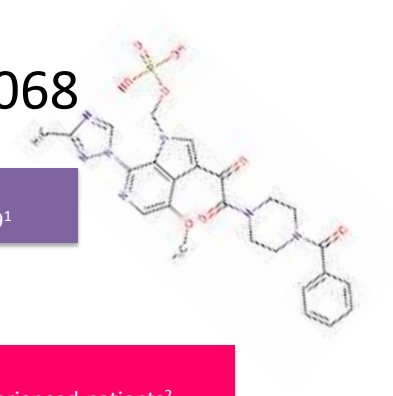
Why are we interested?
Significantly fewer and less severe treatment-emergent CNS AEs than EFV[2,3] and maintains activity in the presence of K103N, Y181C and G190A mutations (in vitro)[4]

Current status?
Phase 2b trial presented in 2015[3], phase 3 trial underway[5]

Target population?
Treatment-naive adults

AE, adverse event; CNS, central nervous system; NNRTI, non-nucleoside reverse transcriptase inhibitor.
1. Anderson et al. Antivir Ther 2015;20:397–405. 2. Gatell et al. J Int AIDS Soc 2014;17:19532. 3. Gatell et al. IAS 2015, Abstract TUAB0104. 4. Lai et al. Antimicrob Agents Chemother 2014;58:1652–63. 5. NCT02275780. Accessed October 2015.

BMS-663068



What is it?
Prodrug of novel attachment inhibitor BMS-626529[1]

Administration?
Oral[1]

Why are we interested?
Potential for new option for heavily treatment-experienced patients[2]

Current status?
Phase 2 published in 2015[2], phase 3 ongoing[3]

Target population?
Heavily treatment-experienced patients[3]
A unique resistance profile, and no in vitro cross-resistance has been observed with other classes

1. Langley et al. Proteins 2015;83:331–50. 2. Lalezari et al. Lancet HIV 2015;2:e427–37. 3. NCT02362503. Accessed October 2015.

BMS-955176

What is it?
Second-generation Maturation Inhibitor

Administration?
Oral QD

Why are we interested?
Potential new option for novel drug combinations
Potential new option for naive and experienced patients[1,2]

Current status?
Proof-of-concept study presented in 2015,[1,2] phase 2b underway[3]

Target population?
Treatment-naive and -experienced patients[3]

1. Hwang et al. CROI 2015, Abstract 114LB. 2. Hwang et al. IAS 2015, Abstract TUAB0106LB. 3. NCT02415595 and NCT02386098. Accessed October 2015.

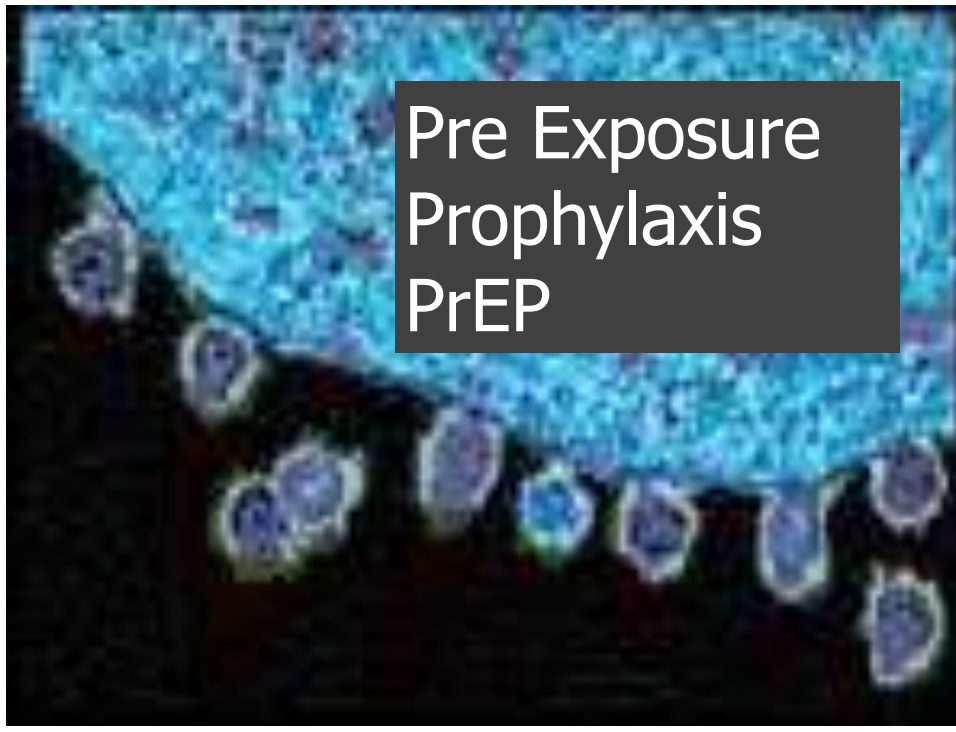
Other strategies…

Monotherapy
Protease inhibitors
Integrase inihibitors ..DTG ?

Intermittent ARV
Study 4D

Bitherapy
3TC + II or PI, II+PI…

Reduction dose
Boosted PI
NNRTI



What is PrEP to prevent HIV infection?

- The **ongoing** use of one or two antiretrovirals by HIV-negative individuals starting **before** an exposure and continuing **afterwards**
  - A potential option to prevent infection from ongoing exposures to HIV during periods of risk

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Potential types of PrEP

How are the antiretrovirals used?	• Oral pill
	• Topical gel (microbicide)
	  •Rectal
	  •Vaginal
	• Injection
	• Intravaginal ring

How often are the antiretrovirals used?	• Daily • Intermittently • Coitally (before/sex)
How many antiretrovirals are used?	• Single • Combination

What concerns does the use of PrEP raise?

- Side-effects and toxicity
- Drug resistance
- Adherence
- Risk compensation
- Access
- Cost

55

What do we know about PrEP?

- In combination with a comprehensive package of prevention services…
    1. Daily TDF/FTC to reduce the risk of infection when used by
        - MSM and trans women
        - Heterosexual men and women
    2. Daily TDF reduced the risk of infection when used by heterosexual men and women
    3. A vaginal tenofovir gel used before and after sex reduced the risk of infection when used by women.
- It needs to be used consistently for it to work.
- The risk of side effects, toxicity, and drug resistance are low.

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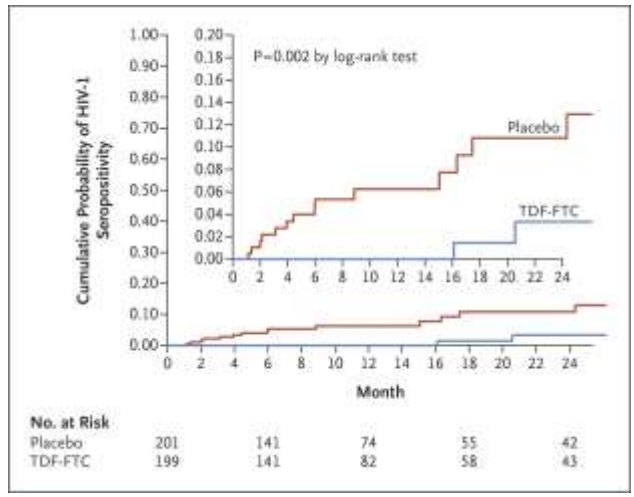
Study Ipergay

- Preexposure prophylaxis with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in men who have sex with men, when it was taken before sexual activity

Molina JM, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Estimates of the Probability of HIV-1 Infection.

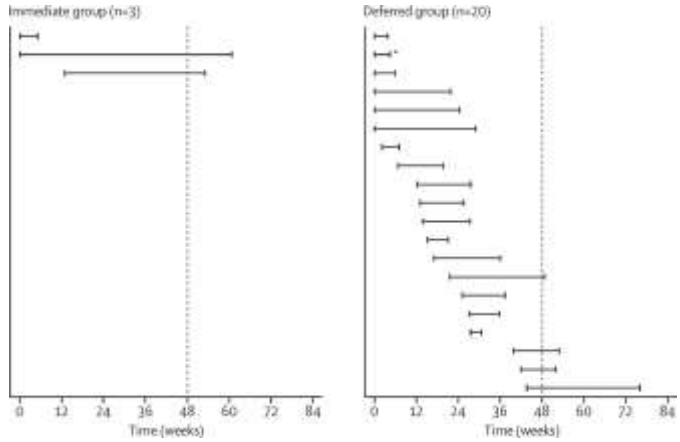


- The use of TDF-FTC before and after sexual activity provided protection against HIV-1 infection in men who have sex with men: 86 % reduction (IC 95 % : 40 - 99 ; p = 0,002)
- The treatment was associated with increased rates of gastrointestinal and renal adverse events

PROUD Study

- Open-label randomised trial enrolled HIV-negative gay and other men who have sex with men who had anal intercourse without a condom in the previous 90 days
- Randomisation 1:1 to receive daily combined tenofovir disoproxil fumarate (245 mg) and emtricitabine (200 mg) either immediately or after a deferral period of 1 year

McCormack S, The Lancet, January 2016



- 3 infections occurred in the immediate group (1·2/100 person-years) versus 20 in the deferred group (9·0/100 person-years)

- Relative-reduction 86%, 90% CI 64–96, p=0·0001

European Guidelines EACS 2015

Pre-exposure Prophylaxis (PrEP)

1. PrEP can be used in adults at high-risk of acquiring HIV infection.

   - Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. A recent STD or use of post-exposure prophylaxis may be markers of increased risk for HIV acquisition.
   - May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV positive partners who are not on treatment.

2. PrEP is a medical intervention that may not provide full protection against acquiring HIV, does not protect against other STDs and should be used in combination with other preventive interventions, including the use of condoms.
   PrEP should be supervised by a doctor, experienced with sexual health and use of HIV medicines, possibly as part of a shared care arrangement.

   The following procedures are recommended:

   - Documented negative fourth generation HIV test prior to starting PrEP. During PrEP, this test should be repeated every 3 months, and PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit.
   - Before PrEP is initiated, HBV serology status should be documented. If HBsAg positive see Clinical Management and Treatment of HBV and HCV Co-Infection in HIV-positive Persons.
   - Counsel that PrEP does not prevent other types of STD; screen for STD (including HCV) when starting PrEP and regularly during use of PrEP.
   - Counsel that PrEP may impact renal and bone health (see page 45 and 41). Check renal function and bone mineral density according to guidelines on TDF use.
   - Counsel that PrEP, like other prevention methods, only works when it is taken. Adherence counselling is recommended.
   - Counsel that PrEP can be prescribed long term but that each consecutive PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring.

3. PrEP regimen

   TDF/FTC 300*/200 mg 1 tablet qd. For MSM with high-risk sexual behavior PrEP may be dosed 'on demand' (double dose of drug 2-24 hours before each sexual intercourse, followed by two single doses of drug, 24 and 48 hours after the first drug intake). If dosed 'on demand', the total dose per week should not exceed 7 tablets.

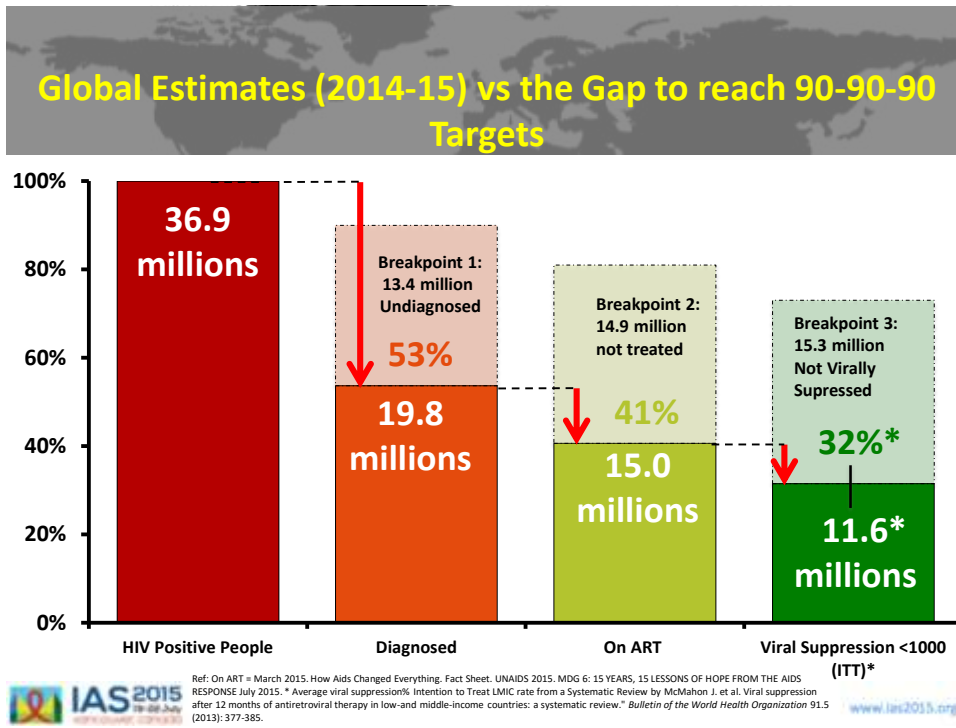
   * In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the concentration of the active metabolite.

To finish…….

90-90-90

An ambitious treatment target to help end the AIDS epidemic

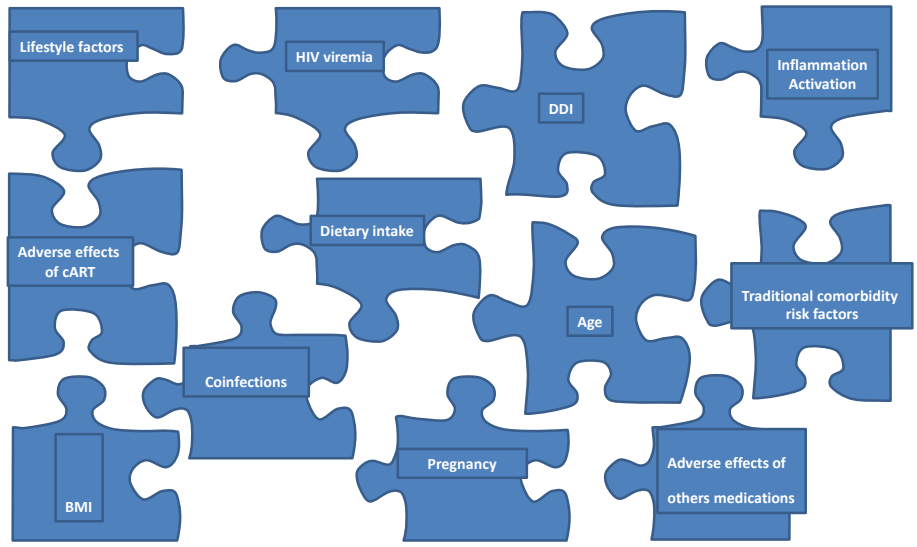
2020



Bridging the gap from current cART to cure

Rasmussen et al. Hum Vaccin Immunother 2013;9:790–9. Katlama et al. Lancet 2013;381:2109–17.

Factors influencing the choice of ART



Conclusions

- Although there are already many HIV drugs in use, new HIV drugs and drugs classes are still being actively developed
- New drugs should aim to have low toxicity, good tolerability and provide novel drug combinations and formulations

Question 1

- Do you want to treat an HIV patient ,with 1 000 CD4 cell counts?

- Yes
- NO

Question 2

- Could you be used integrase inhibitors for all HIV naive adults?
- Yes
- No

Question 3

- Could you be used antiretroviral drugs to prevent HIV infection for high risk acquisition subjects ?
- YES
- NO


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
спасибо
dank je
gracias
tapadh leat
mauruuru
hvala
bedankt
dziękuję
mochchakkeram
go raibh maith agat
obrigado
sukriya
kop khun krap
laikù
arigato
dakujem
grazie
merci
감사합니다
мерси