Actualités en virologie

Paris, le 6 juillet 2011

Journée scientifique de Solthis

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33 Surveillance of Transmitted and Acquired HIV Drug Resistance Using World Health Organization (WHO) Survey Methods in Resource Limited Settings

MR Jordan[1,2], N Parkin[3], and S Bertagnolio[1]

[1]World Health Organization, Geneva, Switzerland; [2]Tufts University School of Medicine, Boston, MA, USA; [3]Data First Consulting, Belmont, CA, USA.

Figure 1. Transmitted Drug Resistance in Recently Infected Populations: Global SDRM[4] Prevalence (N=2788)

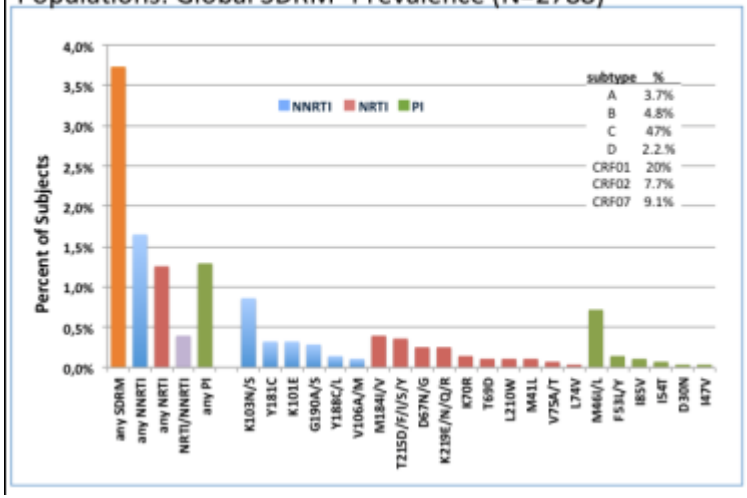


Figure 2. Acquired Drug Resistance at ART Initiation (Baseline): Global SDRM[4] Prevalence (N=1503)

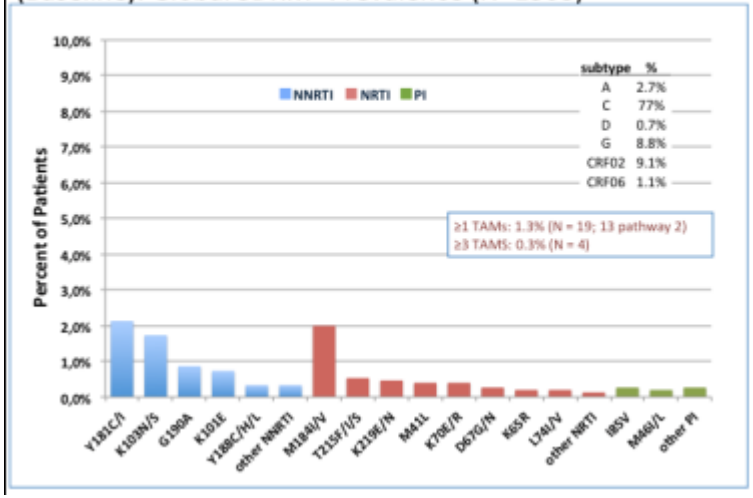
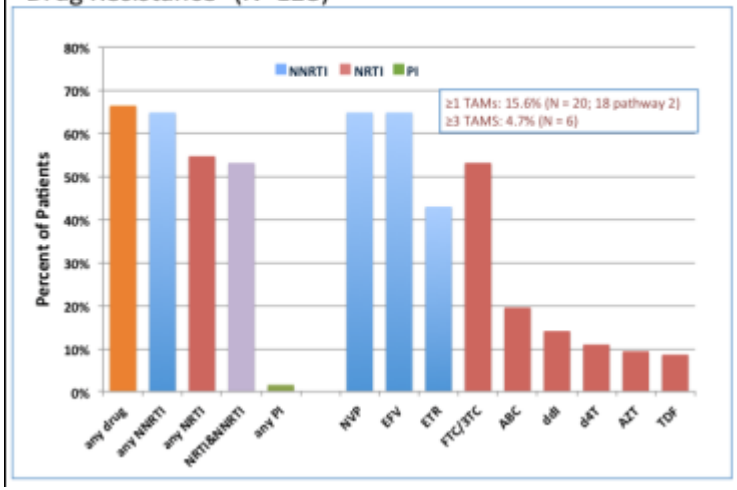


Figure 3. Acquired Drug Resistance (Month 12): Predicted Drug Resistance[6] (N=128)



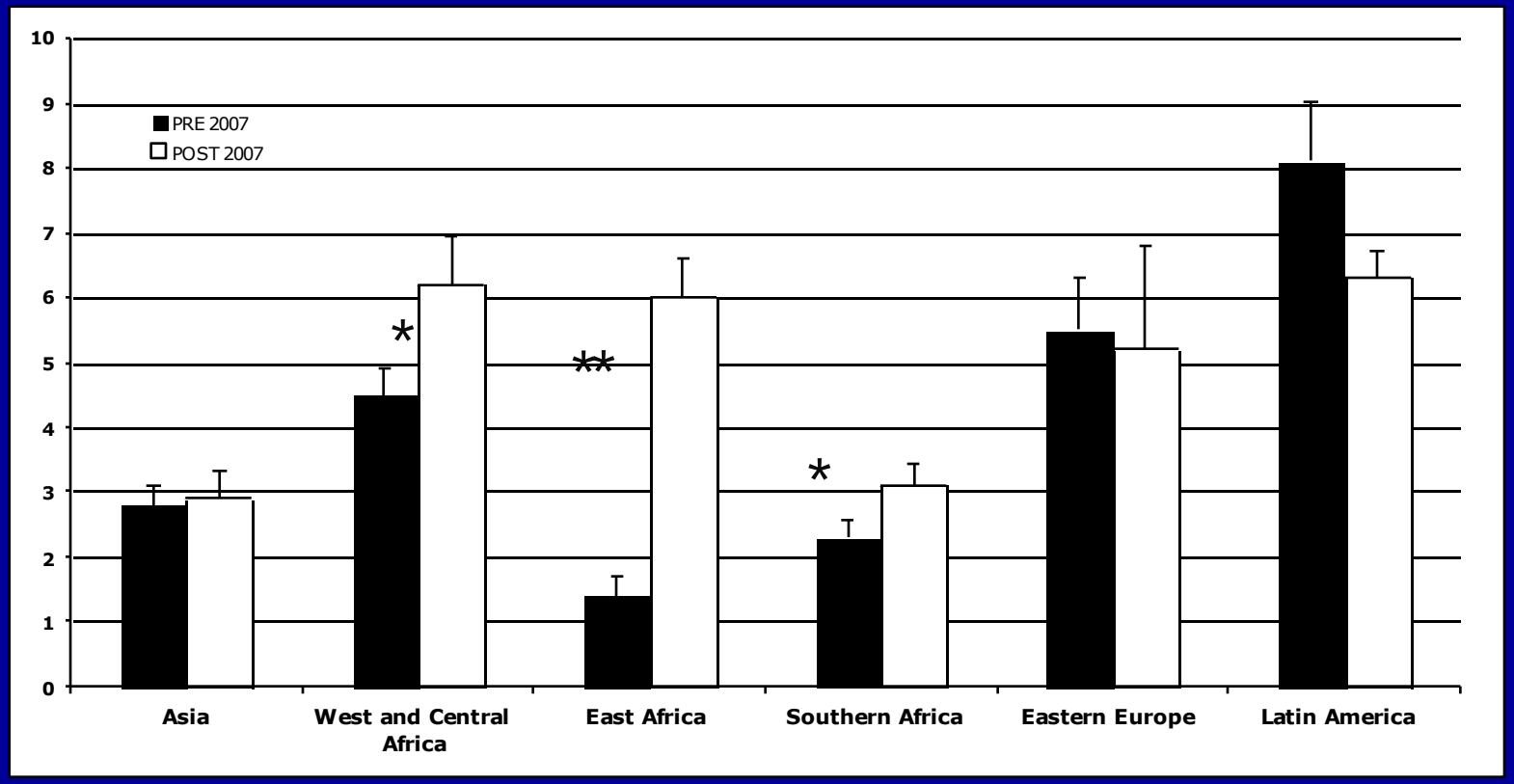
Transmitted Drug Resistance in Low and Middle Income Settings- a meta regression analysis

Ravindra K. Gupta, Binta J. Sultan, Andrew Hill, Tim Haley, Raph Hamers, Deenan Pillay, Michael R. Jordan, Silvia Bertagnolio

UCL

Tufts UNIVERSITY School of Medicine

Prevalence of baseline DRMs pre and post 2007 by region

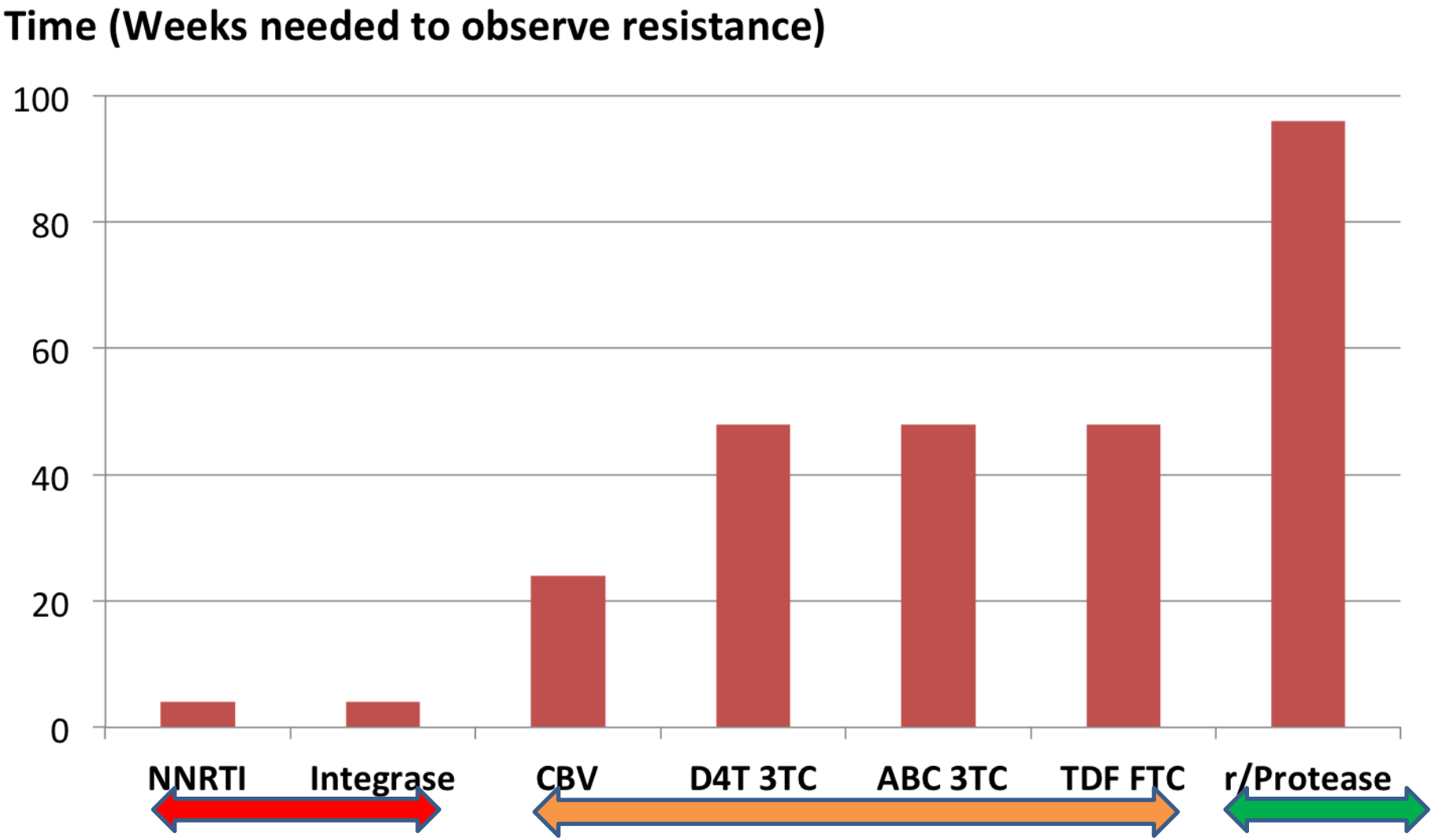


* p<0.05 **p<0.0001

Kinetics of resistance selection = robustness of a drug

- High differences between ARVs families
- Explained by
  - PK characteristics :
    - half life in plasma and in cells
  - Genetic barrier
    - Number of mutations needed to get resistance

Kinetics of resistance selection after the beginning of virological failure
= 3 different behaviors



Expected NRTIs sensitivity spectrum after 1 year of treatment if virological failure

HIV-1

Starting with					
	AZT (Zidovudine)	d4T (Stavudine)	TDF (Tenofovir)	ABC (Abacavir)	ddI (Didanosine)
Cross Resistance ↓					
AZT					
d4T					
TDF					
ABC					
ddI					

- **Opposite behavior between Thymidine analogs (ATZ and d4T) and the others (TDF, ABC and ddI) : these drugs are selecting antagonist mutations**

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Expected NRTIs sensitivity spectrum after 2 years of treatment if virological failure

HIV-1

Starting with	AZT (Zidovudine)	d4T (Stavudine)	TDF (Tenofovir)	ABC (Abacavir)	ddI (Didanosine)
Cross Resistance ↓					
AZT					
d4T					
TDF					
ABC					
ddI					

- TDF,ABC or ddI induce less cross resistance even after a long period of replication
- However after years of replication under AZT or d4T => TDF, ABC and ddI are resistant

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Expected NNRTIs sensitivity spectrum after 1 year of treatment if virological failure

Starting with				
	EFV	NVP	Rilpivirine	ETR
Cross Resistance ↓				
EFV				?
NVP				?
ETR				?

- **Same low genetic barrier and weak robustness of EFV and NVP**
- **ETR (Etravirin) is not affected at least at the beginning if the failure**

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Expected NNRTIs sensitivity spectrum after 2 year of treatment if virological failure

Starting with				
	EFV	NVP	Rilpivirine	ETR
Cross Resistance ↓				
EFV				?
NVP				?
ETR				?

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Expected PIs sensitivity spectrum after 1 year of treatment if virological failure HIV-1

Starting with				
	LPV (Lopinavir)	ATV (Atazanavir)	DRV (Darunavir)	SQV (Saquinavir)
Cross Resistance ↓				
LPV				
ATV				
DRV				
SQV				

- After one year of failure, the sensitivity of LPV is partially affected
- DRV is the most robust PI for the selection of resistance
- ATV does not induce any cross resistance to other PIs

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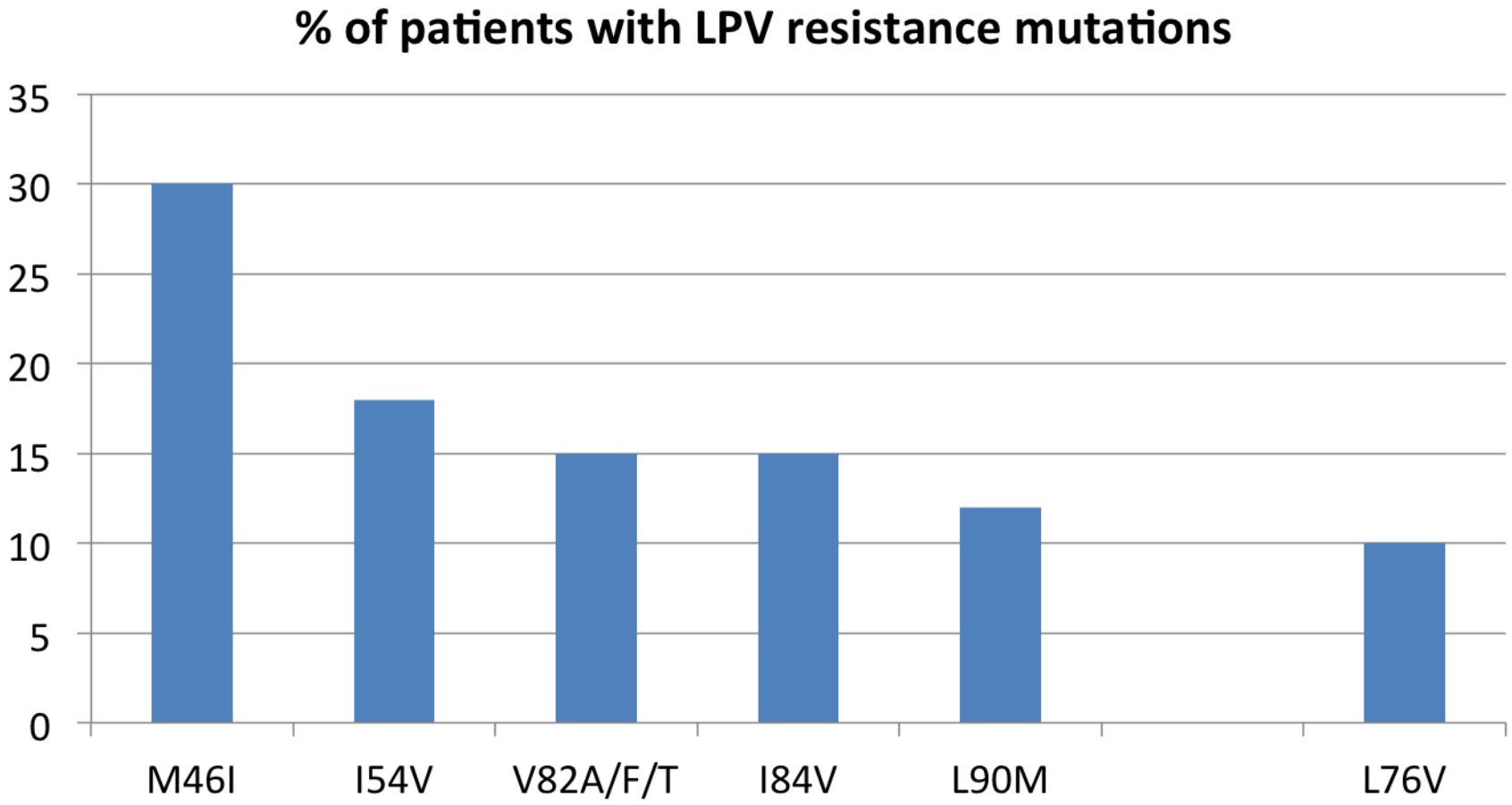
Resistance to LPV after at least one year of use in patients harboring virological failure

A Maiga, University of Bamako, TUPE0127



Expected PIs sensitivity spectrum after 2 years of treatment if virological failure

HIV-1

Starting with				
	LPV (Lopinavir)	ATV (Atazanavir)	DRV (Darunavir)	SQV (Saquinavir)
Cross Resistance ↓				
LPV		?		
ATV				
DRV		?	?	
SQV		?		

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Remaining therapeutic options after first line virological failure

First line		Short term	Long term
NNRTI	AZT/d4T	(TDF, ABC, ddI) + r/PI	(LPV/DRV) + RAL ?
NNRTI	TDF/ABC/ddI	(TDF, ABC, ddI) + r/PI	AZT + r/PI
r/PI	AZT/d4T	(TDF, ABC, ddI) + r/PI	DRV + NNRTIs ? DRV + RAL ?
r/PI	TDF/ABC/ddI	(TDF, ABC, ddI) + r/DRV	DRV + NNRTIs ? DRV + RAL ?

Starting with boosted PI regimens offers more validated second line options in at least short term virological failure

HIV-2

- **Low number of virology labs doing viral load and resistance testing**
- **Cross resistance ++++ of NRTIs**
  - **In most cases selection of K65R even with AZT and d4T**
- **Natural resistance for NNRTIs (EFV, NVP, ETR)**
- **Limited number of active PIs**
  - **Only LPV and DRV are active (+/- Saquinavir)**
- **High activity of Raltegravir but weak robustness**
  - **Same kinetic and resistance pathways than HIV-1**

HIV-2

- **Probably only 2 lines of treatment**
  - **If starting with:**
    - **2 NRTIs + LPV => DRV + RAL**
    - **2 NRTIs + RAL => LPV, DRV mono ?**
      => LPV + SQV ?

General considerations (1)

- Need for viral load testing at least once a year
  - Change earlier for second line
  - Differ the use of broad spectrum active drug (Darunavir, Etravirine) or new class drug (Raltegravir)
- Use preferentially drugs that induce less resistance
  - Boosted PIs in first line ++
- Use preferentially in first line drugs that induce less cross resistance
  - NRTIs : TDF, ABC
  - r/PIs : Atazanavir

General considerations (2)

- It will be very difficult to set up resistance testing everywhere
  - Need to change the treatment using a probabilistic approach

=> Train more physicians and health workers about:

  - Spectrum of activity of drugs against resistant HIV strains


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Grand Merci!

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