Sistema Socio Sanitario
Regione Lombardia
ASST Ovest Milanese

Una giovane paziente con trasmissione verticale

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La paziente

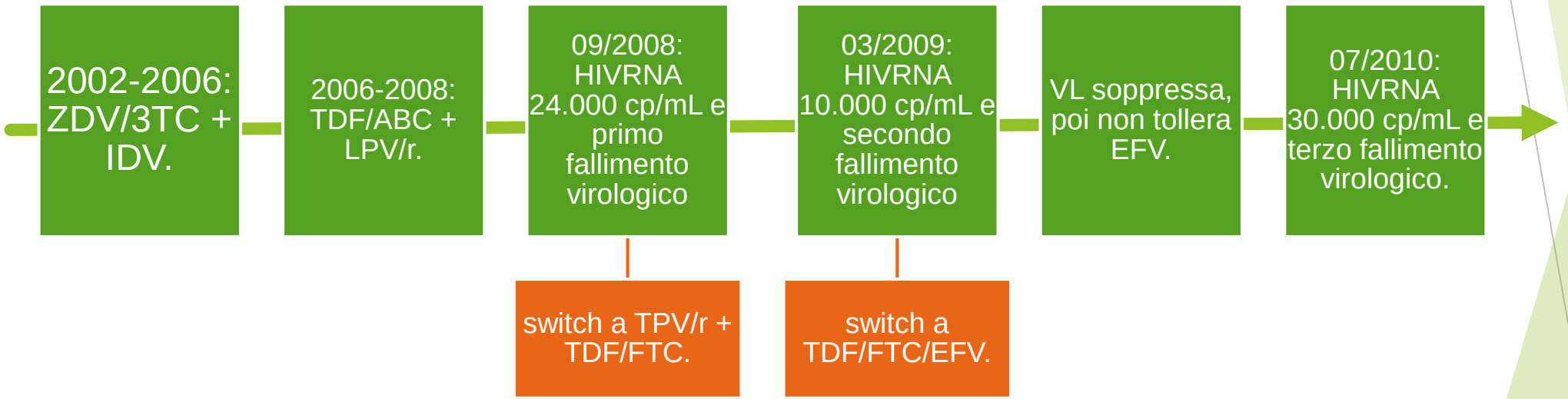
M.S. è una giovane donna romena di 33 anni, seguita per coinfezione da HIV/HBV

- Vive in campo nomadi e torna regolarmente in Romania
- HIV noto dal 1999
- HBV noto dal 2002

Criticità:

- Scarsissima aderenza → resistenze
- Scarso recupero dei CD4 → infezioni opportunistiche

2002-2010


2002-2006: ZDV/3TC + IDV.
2006-2008: TDF/ABC + LPV/r.
09/2008: HIVRNA 24.000 cp/mL e primo fallimento virologico
switch a TPV/r + TDF/FTC.
03/2009: HIVRNA 10.000 cp/mL e secondo fallimento virologico
switch a TDF/FTC/EFV.
VL soppressa, poi non tollera EFV.
07/2010: HIVRNA 30.000 cp/mL e terzo fallimento virologico.

Che cosa ci dice il genotipo?

HIV-1 gruppo M e sottotipo F1
(estremamente
Romania), tropi

Mutazioni selez
anni (al 2010):

- PI: L10V, M4
- RT: D67N, K
  K219Q, V90I
  P225K

Terapia di sal
TDF/FTC, DRV
bid, MVC 1

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A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people

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Abstract

Although, single tablet regimen (STR) efavirenz, emtricibine, and tenofovir disoproxil fumarate (EFV/FTC/TDF) may be appealing in HIV infected persons who are at high risk for non-adherence, the degree to which this simplified formulation affects adherence is not known. The virologic effectiveness of this STR in a potentially non-adherent population remains a concern, given the rapid selection of drug-resistance seen with these drugs. We performed a prospective observational study assessing adherence and virologic response to EFV/FTC/TDF STR among a cohort of homeless and marginally housed individuals. We compared adherence and viral suppression to historical controls followed in the same cohort. Adherence was higher in EFV/FTC/TDF STR regimen compared to non-one-pill once daily therapy (p=0.0060) after controlling for multiple confounders. Viral suppression (HIV RNA <50 c/ml) was greater in EFV/FTC/TDF STR than non-one pill daily regimens (69.2% vs 46.5%; p=0.02), but there was no difference in viral suppression after controlling for adherence. Once daily EFV/TNF/FTC STR appears to be a reasonable option for individuals with multiple barriers to adherence. Randomized clinical trials addressing various therapeutic strategies for this patient population are needed.

Characterization of Human Immunodeficiency Virus Type 1 Isolates from Children in Romania: Identification of a New

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e Inhibitors

Intermediate Resistance
Susceptible
Intermediate Resistance

e Transcriptase Inhibitors

High-Level Resistance
Intermediate Resistance
High-Level Resistance
High-Level Resistance
Low-Level Resistance

se Transcriptase Inhibitors

Susceptible
High-Level Resistance
Susceptible
High-Level Resistance
Susceptible

2010-2015

- 2010-14: buona tolleranza della terapia che assume con discreta compliance (**CD4 compresi tra 450-750/mcL, HIVRNA <37 cp/mL**).

Nel 2010 e 2011 ha 2 IVG

- posiziona IUD e tratta condilomatosi vaginale e anale

Nel 2013 è ricoverata tre volte per polmonite

- viene posta diagnosi di linfangioleiomiomatosi per cui inizia follow-up.

Nel 2015 torna in Romania e rimane senza TARV.

A novembre torna in Italia: gravindex positivo, **HIVRNA 21770 cp/mL e CD4 755 → 103/mcL, HBVDNA 1793469 cp/mL.**

- Ricomincia la TARV introducendo RAL 400 bid
- Aprile 2016 HBVDNA neg HIVRNA 534 cp/mL CD4 250/mcL

Che cosa ci dice il genotipo?

Si confermano le seguenti mutazioni:

- PI: L10V, M46L
- RT: D67N, K219Q

Ma compaiono

- INSTI: L74M

RAL 400 bid → della TARV inv… TDM dei singoli… l'esposizione … bambino.

Il bambino nasce con … ZDV ev intrapartum e riceve l'abituale profilassi con ZDV, 3TC, NVP → NEGATIVO!!

Protease Inhibitors

atazanavir/r (ATV/r)	Potential Low-Level Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Potential Low-Level Resistance

Nucleoside Reverse Transcriptase Inhibitors

…el Resistance

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…Postpartum

…avir in

…el Resistance

…n,[1] V Hillewaert[1] and

…ss for unbound
…iavir/ritonavir
…iant women.

…sceptible
…tential Low-Level Resistance
…sceptible
…tential Low-Level Resistance

raltegravir (RAL) Potential Low-Level Resistance

Maraviroc Pharmacokinetics in HIV-1–Infected Pregnant Women

Angela Colbers,[1] Brookie Best,[4] Stein Schalkwijk,[1,2] Jiajia Wang,[6] Alice Stek,[5] Carmen Hidalgo Tenorio,[10] David Hawkins,[11] Graham Taylor,[12] Regis Kreitchmann,[13] Sandra Burchett,[7] Annette Haberl,[14] Kabamba Kabeya,[15] Marjo van Kasteren,[3] Elizabeth Smith,[9] Edmund Capparelli,[4] David Burger,[1] and Mark Mirochnick[8]; for the PANNA Network and the IMPAACT 1026 Study Team

Conclusions. Overall maraviroc exposure during pregnancy was decreased, with a reduction in AUC_{tau} and maximum concentration of about 30%. C_{trough} was reduced by 15% but exceeded the minimum C_{trough} target concentration. Therefore, the standard adult dose seems sufficient in pregnancy.

should be considered in pregnant women with high weight (> 90 kg) or inadequate HIV RNA response.

Keywords: antiretrovirals, HIV, pregnancy, prevention of perinatal transmission, tenofovir

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2016-2019

Sospende TARV da dicembre 2016 a maggio 2017	• passaggio da Infettivologia Pediatrica ai nostri Ambulatori e ripresa della precedente TARV.
12/2017: **CD4 43/mcL e HIVRNA 7560 cp/mL**	• diagnosi di **NTM da MAC** → azitromicina, rifabutina e etambutolo
10/2018: gravindex positivo → **cambia TARV a RAL 400 bid + DRV/r bid + MVC + TDF.**	• 12/2018: inizia profilassi secondaria con azitromicina + etambutolo • IVG e stop TARV
03-04/2019: **CD4 31/mcL, HIVRNA 14.000 cp/mL**	• diagnosi di **neuroyoxoplasmosi** (lesione emisferica sx) → sulfadiazina + pirimetamina, poi TMP/SMX

Che cosa ci dice il genotipo?

Tra il 2017 e il 2019 si confermano:

- PI: L10V, K20R, M36I, M46L, V82A
- RT: D67N, T69A, K219Q
- INSTI: L74M

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Potential Low-Level Resistance
zidovudine (AZT)	Low-Level Resistance
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Potential Low-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT comments

NRTI

- **D67N** is a non-polymorphic TAM associated with low-level resistance to AZT and d4T. When present with other TAMs, it contributes reduced susceptibility to ABC, ddI, and TDF.
- **K219Q/E** are accessory TAMS associated with reduced susceptibility to AZT and possibly d4T.

Other

- **T69S/A/I/E** are relatively polymorphic mutations weakly selected in patients receiving NRTIs. Their effects on NRTI susceptibility have not been well studied.

Protease Inhibitors	
atazanavir/r (ATV/r)	Intermediate Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Intermediate Resistance

PR comments

PI Major

- **M46I/L** are relatively non-polymorphic PI-selected mutations. In combination with other PI-resistance mutations, they are associated with reduced susceptibility to each of the PIs except DRV.
- **V82A** is a non-polymorphic mutation selected primarily by IDV and LPV. It reduces susceptibility to these PIs and contributes cross-resistance to each of the remaining PIs except DRV and TPV.

Other

- **L10I/V** are polymorphic, PI-selected accessory mutations that increase the replication of viruses with other PI-resistance mutations.
- **K20R** is a highly polymorphic PI-selected accessory mutation.

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	Susceptible
cabotegravir (CAB)	Susceptible
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Susceptible
raltegravir (RAL)	Susceptible

IN comments

Other

- **L74M** is a polymorphic accessory mutations commonly selected by each of the INSTIs. In ARV-naive patients, **L74M** occurs in 0.5% to 5% of patients depending on subtype. L74I occurs in 4% to 40% of patients depending on subtype. L74I is the consensus amino acid for subtype A6 and does not appear to be selected by INSTI therapy. Alone, **L74M/I** have minimal, if any, effect on INSTI susceptibility. However, **L74M** and possibly L74I reduce susceptibility to each of the INSTIs when they occur with major INSTI-resistance mutations. L74F is a rare nonpolymorphic mutation which also contributes reduced susceptibility when it occurs with other INSTI-resistance mutations.

2020-2021

01/2020: CD4>200 (stop TMP/SMX) e HIVRNA 350 cp/mL

- Semplifica per migliorare la compliance a DTG + DRV/c/FTC/TAF
- Non tollera il cobicistat (nausea, disturbi GI) → torna a DTG, DRV/r bid + TDF con discreto controllo (CD4 > 250, HIVRNA < 50 cp/mL)

06/2021: gravida 20ma settimana

- Switch a RAL 400 bid + TDF/FTC + DRV/r bid
- Arriva al parto a ottobre 2021 soppressa

E poi? …Keypoints

- Ricordiamo le resistenze archiviate!
- Necessità di mantenere la copertura per HBV
- Avvicinarsi all’STR

Grazie per l’attenzione