HIV in Europe 2020 – What will it look like?

Carlo Federico Perno

Rome, 25th May 2016

14th European Meeting on HIV & Hepatitis 2016
Emergence of acquired HIV-1 drug resistance has almost been stopped in Switzerland: a 15 year prospective cohort analysis


**Background:** Drug resistance is a major barrier to successful antiretroviral treatment (ART). Therefore, it is important to monitor time trends at a population level.

**Methods:** We included 11,084 ART-experienced patients from the Swiss HIV Cohort Study (SHCS) between 1999 and 2013. The SHCS is highly representative and includes 72% of patients receiving ART in Switzerland. Drug resistance was defined as the presence of at least one major mutation in a genotypic resistance test. To estimate the prevalence of drug resistance, data for patients with no resistance test was imputed based on patient’s risk of harboring drug resistant viruses.

**Results:** The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013. The upper estimated prevalence limit of drug resistance among ART experienced patients decreased from 57.0% in 1999 to 37.1% in 2013. The prevalence of three-class resistance decreased from 9.0% to 4.4% and was always <0.4% for patients who initiated ART after 2006. Most patients actively participating in the SHCS in 2013 with drug resistant viruses initiated ART before 1999 (59.8%). Nevertheless, in 2013, 94.5% of patients who initiated ART before 1999 had good remaining treatment options based on Stanford algorithm.

**Conclusion:** HIV-1 drug resistance among ART-experienced patients in Switzerland is a well-controlled relic from the pre-combination ART era. **Emergence of drug resistance can be virtually stopped with new potent therapies and close monitoring.**

Clinical Infectious Diseases published March 8, 2016
The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013.
The prevalence of resistance to 3 classes significantly decreased over the years, from 30.5% before 2001 to 4.2% in 2015, while the prevalence of sequences without resistance significantly increased from 12.9% before 2001 to 61.1% in 2015.

Analysis performed on 9,507 sequences of treated HIV-1 infected patients from protease and reverse transcriptase genes. P-values by Chi-squared test for trend. *Update July 2015.

Di Carlo, Armenia, and Santoro, unpublished data
Clinical case: ID 18

- Sex: Man
- Age: 53 years
- Risk Factor: MSM
- CDC: C3
- First HIV-1 seropositivity: August 1997

Viro-immunological data at diagnosis:
- CD4: 130 cells/µl
- VL: 400,000 cps/ml
Drugs administered from September 1997 to July 2014:

- **NRTI**  AZT DDC DDI D4T TDF FTC 3TC
- **NNRTI**  EFV NVP ETR
- **PI**  ATV DRV SQV IDV NFV LPV RTV FPV
- **INI**  RAL
- **FI**  T20
Clinical Case: ID 18 Patient infected with HIV-1 B subtype


**Risk Factor:** MSM

**Clinical Case: ID 18 Patient infected with HIV-1 B subtype**

**Age:** 53  
**Sex:** M  
**Risk Factor:** MSM  
**CDC:** C3  
**1st Seropositivity:** Aug-1997

**CD4 cell count (cells/µl)**

- **GRT July 2014**  
  - VL: 507,041 cps/ml  
  - CD4: 70 cells/µl  
  - PR: L10I K20R V32I L33F M36I K43T M46I I54L D60E I62V L63P A71V L76V V82A I84V I93L  
  - RT: K65KR D67DG K70EK Y181C M184V  
  - INT: None

- **GRT January 2015**  
  - VL: 414,403 cps/ml  
  - CD4: 38 cells/µl  
  - PR: L10I K20R V32I L33F M36I K43T M46I I54L A71V L76V V82A I84V I93L  
  - RT: D67DG K70EK Y181I  
  - INT: G140S Q148H

- **GRT April 2016**  
  - VL: 23,867 cps/ml  
  - CD4: 141 cells/µl  
  - PR: L10I K20R V32I L33F M36I K43T M46I I54L D60E I62V L63P A71V L76V V82A I84V, I93L  
  - RT: K65KR D67DG K70EK Y181I  
  - INT: None

**Viremia (log copies/ml)**

- **MAR 13 – JUL 14**  
  - TDF/FTC + DRV/r (800/100)

- **AUG 14 – JAN 15**  
  - ETR RAL DRV/r (800/100)

- **FEBR 15 – JAN 16**  
  - AZT 3TC DRV/r (600/100) DTG

- **FEBR 16 – APR 16**  
  - ETR AZT 3TC DRV/r (600/100)
Settings with Viral load Monitoring and Multiple Treatment Options

Viremic patients with multi-drug resistant HIV-1

Patients currently suppressed on therapy That have multi-drug resistant HIV-1

Joe Eron, CROI 2016
RESISTANT HIV-1 WILL ALWAYS BE WITH US

Four to eight decades of therapy!
Previous exposure to suboptimal treatment developed world
Limited monitoring of virologic response world-wide
Transmitted drug resistance
Today, thanks to the modern potent regimens, more than 90% of patients starting a first-line regimen achieve virological suppression.

Indeed…….
By 72 weeks of therapy, the probability of virological success was 96.8%.

Median time (95% CI) of achieving VS (weeks)
--- 18 (17 – 18)

By 72 weeks of therapy, the probability of virological success was 96.8%.

Median time (95% CI) of achieving VS (weeks)
--- 18 (17 – 18)

Patients (N=1,734) followed after HAART starting regardless therapy changes or interruptions. CI: confidence interval. HAART: highly active antiretroviral therapy. VS: virological success.
By 72 weeks of therapy, patients having pre-HAART viremia >500,000 copies/mL showed the lowest probability of achieving VS compared to others pre-HAART viremia ranges.

Patients (N=1,734) followed after HAART starting regardless therapy changes or interruptions. CI: confidence interval. HAART: highly active antiretroviral therapy. <30K: <30,000. 30-100K: 30,000-100,000. 100-300K: 100,000-300,000. 300-500K: 300,000-500,000. >500K: >500,000. VS: virological success.

Di Carlo, Armenia and Santoro, unpublished data
Clinical Case: ID 6784 Patient infected with HIV-1 B subtype
Risk Factor: MSM
1st Seropositivity: January 2001
Age: 35
Sex: M
CDC stage: B2

From January 2001 to August 2010
Drug naïve

On August 2010
Viremia: 138,335 copies/ml
CD4: 118 cells/µl

From Sept 2010 to Jan 2012
GRT August 2010
VL: 138,335 cps/ml

From Jan 2012 to Jul 2015
GRT January 2012
VL: 185 cps/ml

SEPT 10 - JAN 12
TDF+FTC, DRV/r (800/100)

FEB 12 - JUL 15
TDF+FTC, DRV/r (600/100)
Clinical Case: ID 7416 Patient infected with HIV-1 B subtype

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Risk Factor</th>
<th>1st Seropositivity</th>
<th>CDC stage</th>
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<tbody>
<tr>
<td>46</td>
<td>M</td>
<td>MSM</td>
<td>February 2007</td>
<td>A2</td>
</tr>
</tbody>
</table>

GRT FEBRUARY 2008
VL: 215,488 cps/ml CD4: 275 cells/µl
PR: L33F
RT: T215A

Other pol mutations

Viremia (log copies/ml)
CD4 cell count (cells/µl)

FEB 07-08
DRUG NAIVE

MAR 08 - OCT 09
TDF+FTC, DRV/r (600/100)

NOV 09 - NOV 15
TDF+FTC, DRV/r (800/100)
Overall, by 96 weeks after achieving virological success, the probability of virological rebound was 17.5%.

Patients (N=1,671) followed after achieving VS regardless therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. VS: virological success.
By 96 weeks after achieving virological success, patients having pre-HAART viremia >500,000 copies/mL showed the highest probability of experiencing virological rebound compared to other pre-HAART viremia ranges.

Pre-HAART viremia ranges (copies/mL):

- <30K
- 30-100K
- 100-300K
- 300-500K
- >500K

Patients (N=1,671) followed after achieving VS regardless therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. <30K: <30,000. 30-100K: 30,000-100,000. 100-300K: 100,000-300,000. 300-500K: 300,000-500,000. >500K: >500,000. HAART: highly active antiretroviral therapy. VS: virological success.
Patients with pre-existent NRTI+NNRTI resistance had a higher probability of experiencing VR compared to those harboring pre-existent NRTI or NNRTI resistance and to those without pre-existent RTI resistance.

Di Carlo et al., 14th European Meeting on HIV & Hepatitis 2016
Clinical case: ID 1463

• Sex: Man
• Age: 41 years
• Risk Factor: Sexual
• CDC: B2
• First HIV-1 seropositivity: on January 1995
|-------------------------------------------------------------|--------|-------|-------------------|--------|-------------------------------|

Drugs administered from February 1996 to March 2005

- **NRTI** AZT DDC DDI D4T 3TC
- **NNRTI** EFV NVP
- **PI** IDV NFV

- Genotyping Resistance Test on March 2005:
  - CD4: 681 cells/µl; VL: 5,850 cps/ml

Test reveals an infection by a subtype B of HIV-1

- PR: M36I L63P
- RT: M41L K101R Y181C G190AG L210W T215Y K219KN
Clinical Case: ID 1463 Patient infected with HIV-1 B subtype


• From April 2005 to April 2006
  Therapy interruption

• Genotyping Resistance Test on April 2006:
  CD4: 383 cells/µl; VL: >500,000 cps/ml
  - PR: M36I L63P
  - RT: K101R Y181CY T215AT

May 2006: Therapy with Abacavir + 3TC + Atazanavir/r is started
Clinical Case: ID 1463 Patient infected with HIV-1 B subtype
Age: 41
Sex: M
Risk Factor: Sexual
CDC: B2
1st Seropositivity: January 1995

GRT April 2006
VL: <50 cps/ml
CD4: 383 cells/µl
PR: M36I L63P
RT: K101R Y181CY T215AT

GRT March 2005
- PR: M36I L63P
- RT: M41L K101R Y181C G190AG L210W T215Y K219KN

GRT February 2016
VL: 1,574 cps/ml
CD4: 697 cells/µl
PR: M36I L63P A71V
RT: M41L K101R V106I Y181C M184V L210W T215Y K219N
INT: NONE

Other pol mutations
PR: T12K I15V E35D I62V E65D K70T I72V V75I
RT: D121Y K122E I135T S162C D177E K223T L228R A272P K277R V292I Q334N

MAY 06 – MAR 15
ABC 3TC ATV/r

APR 15 – FEB 16
TDF/FTC/RPV
Substantial **resistance** is observed at low viremia after first-line failures.

*First line failure*

![Graph showing prevalence of at least 1 MRM according to drug class and viremia levels.]

- Patients under NRTI (N=507)
- Patients under NNRTI (N=165)
- Patients under ritonavir-boosted PI (N=188)

MRM: major resistance mutation.

*Santoro et al. CROI 2014; CID 2014*
INSTI genotypic susceptibility scores (GSS) according to viremia levels in 156 samples from patients failing a raltegravir containing regimen.

Overall 36.4% and 28.3% of samples showed resistant GSS for raltegravir and elvitegravir, respectively. By stratifying GSS scores according to viremia levels the proportion of samples showing raltegravir resistance significantly varied according with viremia levels (p=0.030)
Background: The clinical implications of emergent HIV drug resistance on samples with low-level viraemia (LLV <1000 copies/ml) remain unclear. We undertook the present analysis to evaluate the impact of emergent HIV drug resistance at LLV on the risk of subsequent virologic failure.

Methods: One thousand nine hundred and sixty-five patients had genotype results at LLV. Risk of virologic failure (1000 copies/ml) after LLV was evaluated by Kaplan–Meier analysis and Cox proportional hazards regression. Resistance was assessed using the Stanford algorithm or virtual phenotypes. Patients were grouped into four susceptibility categories (‘GSS’ or ‘vPSS’) during LLV, corresponding to the number of ‘active’ drugs prescribed: <1; 1–1.5; 2–2.5; and 3.

Results: A total of 1702 patients with follow-up on constant therapy were eligible for analysis. Participants excluded due to changing therapy or loss to follow-up before their next observation had mostly similar characteristics to included participants. There was a ‘dose-dependent’ increase in the hazard ratio for virologic failure with susceptibility categories at LLV. Compared with a GSS of at least 3, hazard ratios for virologic failure were 1.4 for GSS 2–2.5; 2.0 for GSS 1–1.5; and 3.0 for GSS less than 1 (P<0.001). Numerous sensitivity analyses confirmed these findings.

Conclusion: Our results demonstrate that emergent HIV drug resistance at LLV is strongly associated with subsequent virologic failure. Furthermore, we uncovered a ‘dose-dependent’ increase in the hazard ratio for virologic failure with decreasing GSS estimated at the time of LLV. On the basis of these findings, we propose that resistance genotyping be encouraged for HIV-infected individuals on antiretroviral therapy experiencing low-level viraemia.
Virologic failure was faster and more common in patients with lower genotypic susceptibility scores during low-level viraemia.

Kaplan–Meier curves for the proportion of patients remaining on the same therapy with viral loads <1000 copies/ml following their first low-level viraemia (LLV) episode. Patients are divided into four groups according to their GSS, and followed for up to 5 years while remaining on constant therapy.

Swenson et al., AIDS 2014
TRANSMITTED DRUG RESISTANCE
Studies carried out in Europe and America highlight the current (and future) important role of transmission clusters in the spread of TDR.

- Fabeni et al. Dynamics of Transmitted HIV-1 Drug Resistance according to Subtype in Italy over the years 2000-2014. XXV IWHDR 2016, Abstract 74.
- Harrigan PR et al. Large-Scale Transmission and Clustering of HIV Protease Resistance in Ontario, Canada. CROI 2016, Abstract 491LB.
High level protease inhibitor resistance can occur with sufficient replicative fitness to circulate for more than a decade in the community, suggesting the potential for transmission of extensively drug resistant HIV, which could threaten our treatment paradigms.

Systematic surveillance of HIV resistance in untreated individuals remains important, even as the incidence of resistance in treated populations declines overall.
Recent Transmission Clustering of HIV-1 C and CRF17_BF Strains Characterized by NNRTI-Related Mutations among Newly Diagnosed Men in Central Italy

Background
Increased evidence of relevant HIV-1 epidemic transmission in European countries is being reported, with an increased circulation of non-B-subtypes. Here, we present two recent HIV-1 non-B transmission clusters characterized by NNRTI-related amino-acidic mutations among newly diagnosed HIV-1 infected men, living in Rome (Central-Italy).

Methods
Pol and V3 sequences were available at the time of diagnosis for all individuals. Maximum-Likelihood and Bayesian phylogenetic-trees with bootstrap and Bayesian-probability supports defined transmission-clusters. HIV-1 drug-resistance and V3-tropism were also evaluated.

Results
Among 534 new HIV-1 non-B cases, diagnosed from 2011 to 2014, in Central-Italy, 35 carried virus gathering in two distinct clusters, including 27 HIV-1 C and 8 CRF17_BF subtypes, respectively. Both clusters were centralized in Rome, and their origin was estimated to have been after 2007. All individuals within both clusters were males and 37.1% of them had been recently-infected. While C-cluster was entirely composed by Italian men-who-have-sex-with-men, with a median-age of 34 years (IQR:30–39), individuals in CRF17_BF-cluster were older, with a median-age of 51 years (IQR:48–59) and almost all reported sexual-contacts with men and women. All carried R5-tropic viruses, with evidence of atypical or resistance amino-acidic mutations related to NNRTI-drugs (K103Q in C-cluster, and K101E+E138K in CRF17_BF-cluster).

Conclusions
These two epidemiological clusters provided evidence of a strong and recent circulation of C and CRF17_BF strains in central Italy, characterized by NNRTI-related mutations among men engaging in high-risk behaviours. These findings underline the role of molecular epidemiology in identifying groups at increased risk of HIV-1 transmission, and in enhancing additional prevention efforts.
Prevalence of transmitted drug resistance by geographical region

- Major and statistically significant geographical variation in patterns of TDR was observed.
- Most strikingly, the overall prevalence of TDR was markedly higher in the USA (12.6%) than Europe (8.8%), driven by higher rates of NNRTI-related mutations (8.4% vs. 3.4%; $P < 0.001$).
The prevalence of TDRM is stable in Europe

Hofstra et al, IDRW 2016
Non-B infected patients accounted for 30.8% (N=1,331) of the overall population.

Overall, an increase over time of non-B infected patients was found (<2005-2014: 19.5%-38.5%, p<0.0001*) (a).

Non-B subtypes progressively raised in Italians (<2005-2014: 6.5%-28.8%, p<0.0001*) (b).

*By Chi-squared test for trend.
Among 2,992 B subtype infected patients analysed, TDR to any drug class decreased over time with a trend toward significance (<2005-2014: 13.4%-8.1%, p=0.137*). PI TDR significantly decreased over time (<2005-2014: 5.0%-1.6%, p<0.001*).

Among 1,331 non-B subtype infected patients analysed, TDR to any drug class increased over time with a trend toward significance (<2005-2014: 2%-7.1%, p=0.150*).
Patients with isolated NNRTI TDR experienced low VF rates with INSTIs, and intermediate with bPIs.

In the as-treated analysis, by 100 weeks of treatment, VF occurred in 15% (n=8), 2% (n=1) and 25% (n=4) of patients in the bPI, INSTI and NNRTI groups, respectively.

The inclusion criterion were:
(i) isolated NNRTI resistance defined as an initial genotype containing one or more NNRTI-associated surveillance drug-resistance mutations (SDRMs) without any NRTI or PI-associated SDRMs and
(ii) treatment with a standard regimen defined as a dual NRTI backbone plus a bPI, INSTI or NNRTI received by two or more patients with isolated NNRTI resistance.

Analysis on 131/3,245 (4.%) patients with isolated TDR.

Figure 1. Kaplan Meier plot of As-Treated and ITT failure outcomes by base-drug class.

Clutter et al., JAIDS 2016
Clinical case ID 1848

Age: 44 years old

Sex: Female

Risk Factor: Heterosexual

CDC stage: A

HIV-1 subtype: B

First seropositivity: January 1995
Clinical Case: ID 1848 Patient infected with HIV-1 CRF05_DF subtype

<table>
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<th>Sex:</th>
<th>Risk Factor:</th>
<th>CDC:</th>
<th>1st Seropositivity:</th>
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<td>44</td>
<td>F</td>
<td>Heterosexual</td>
<td>A</td>
<td>January 1995</td>
</tr>
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</table>

Drugs received: from January 1995 to May 2004

**NRTI:** AZT DDI D4T TDF 3TC  
**NNRTI:** EFV NVP  
**PI:** None

On May 2004

- **VL** 274,953 cps/ml  
- **CD4** 360 cells/µl

Genotypic Resistance Test

**Resistance mutations**

**PR:** L10V  
**RT:** K101KE K103KN V108VI K219KQ

**Other pol mutations**

**PR:** E35D M36IV R41K R57K Q61N E65D I72T L89M  
**RT:** V35T T39TA V60I K102Q K122KR D123E S162SN K166KR K173I Q174K D177E I178IL V179X T200TA Q207AT R211K V245K A272P K281R I293IV E297KPQT S322T
Clinical Case: ID 1848 Patient infected with HIV-1 CRF05_DF subtype

Risk Factor: Heterosexual

Age: 44

Sex: F

CDC: A

1st Seropositivity: January 1995

**CD4 cell count (cells/µl)**

Viremia (log copies/ml)

<table>
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<th>CD4 cell count (cells/µl)</th>
<th>Viremia (log copies/ml)</th>
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</table>

**GRT May 2004**

VL 274,953 cps/ml

CD4 360 cells/µl

**Resistance mutations**

**PR:** L10V

**RT:** K101KE K103KN V108VI K219Q

**Other pol mutations**

**PR:** E35D M36IV R41K R57K Q61N E65D I72T L89M

**RT:** V35T T39TA V60I K102Q K122KR D123E S162SN K166KR K173I Q174K D177E I178IL V179X T200TA Q207AT R211K V245K A272P K281R I293IV E297KPQT S322T

**From June 2004 to January 2016**

TDF 3TC ATV/r
Clinical case: ID 10799

- Sex: Male
- Age: 48 years
- Risk Factor: MSM
- CDC: B
- First HIV-1 seropositivity: 14 September 2010
- Subtype: B

Data at first seropositivity response:
  - CD4: 448 cells/ul
  - VL: >10,000,000 cps/ml
  - Acute infection

September 17th 2010:
  - CD4: 465 cells/ul
  - VL: 170,000,000 cps/ml
Clinical Case: ID 10799 Patient infected with HIV-1 B subtype  
Age: 48  
Sex: M  
Risk Factor: MSM  
CDC: B  
First Seropositivity: Sept-2010

• Genotyping Resistance on the 17th of September 2010:
  - PR: L63A V77I
  - RT: V90I L100I K103N L210W T215D
  GP-120(V3): K10R H13T Y21F T22A I26V D29N
  Tropism*: R5 tropic virus (FPR*: 55.1%)

Other PR-RT mutations
PR: I13V N37C D60E I62V
RT: V35I V60I A98S D121H K122E T139K I142V D177E V179I Q197E A272P K277R I293V P294Q E297K Q334Y
Clinical Case: ID 10799 Patient infected with HIV-1 B subtype

<table>
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<th>Sex</th>
<th>Risk Factor</th>
<th>CDC</th>
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<td>48</td>
<td>M</td>
<td>MSM</td>
<td>B</td>
<td>September-2010</td>
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</table>

Risk Factor:
MSM

Clinical Case: ID 10799 Patient infected with HIV-1 B subtype

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<td>B</td>
<td>September-2010</td>
</tr>
</tbody>
</table>

CD4 cell count (cells/ul)

- September 2010: CD4 = 465 cells/ul
- July 2015: CD4 = 816 cells/ul

Viremia (log copies/ml)

- September 2010: Viremia = 170,000,000 cps/ml
- July 2015: Viremia = 184,933 cps/ml

**Undetectability threshold**

**GRT September 2010**
- VL: 170,000,000 cps/ml
- CD4: 465 cells/ul
- PR: L63A V77I
- RT: V90I L100I K103N L210W T215D
- GP-120(V3): K10R H13T Y21F T22A I26V D29N
- Tropism*: R5 tropic virus (FPR*: 55.1%)

**GRT July 2015**
- VL: 184,933 cps/ml
- CD4: 816 cells/ul
- PR: L10F K20T V32I L33F K43T M46I I47V I54L L63P A71T V77I V82A L89V L90M I93L
- RT: M41L K103N E138G Y181I

**Geno2pheno algorithm**

*Geno2pheno algorithm*
By the arrival of the new wave of integrase inhibitors, a revision of resistance monitoring is crucial.

Knowledge of HIV-1 resistance is continuously evolving.

Results from clinical practice with elvitegravir and dolutegravir are expected to provide additional resistance information.

Stekler et al. Antivir Ther. 2015

✓ We aimed to evaluate the prevalence of transmitted INSTI mutations among persons with primary HIV-1 infection in Seattle, WA, USA

✓ Persons with primary HIV-1 infection have enrolled in an observational cohort at the University of Washington Primary Infection Clinic since 1992. We performed a retrospective analysis of plasma specimens collected prospectively from the 82 antiretroviral-naive subjects who were enrolled from 2007-2013, after FDA-approval of the first INSTI. Resistance testing was performed by consensus sequencing.

✓ Specimens for analysis had been obtained a median of 24 (IQR 18-41, range 8-108) days after the estimated date of HIV-1 infection. All subjects were infected with HIV-1 subtype B except for one subject infected with subtype C. Consensus sequencing identified no subjects with major INSTI mutations (T66I, E92Q, G140S, Y143C/H/R, S147G, Q148H/K/R, N155H).

✓ Although our sample size was small, this study does not support the need at this time to evaluate integrase mutations as part of routine consensus sequencing among persons newly diagnosed with HIV-1 infection.

✓ However, it is likely that the prevalence of transmitted INSTI mutations may increase with the recent commercial introduction of additional INSTIs and presumably greater INSTI use among persons living with HIV-1.
Transmitted resistance to HIV integrase strand-transfer inhibitors: right on schedule

Christopher B. Hurt, MD [Clinical Assistant Professor]
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Abstract

Transmitted drug resistance (TDR), the primary acquisition of an HIV variant already resistant to antiretrovirals, impacts approximately 15% of all new infections in the United States. Historically, from the time initial agents in the reverse transcriptase, protease, and entry inhibitor classes were introduced, it took three to five years before the first case reports of TDR appeared. With the description of the first two cases of transmitted integrase strand-transfer inhibitor resistance, it is only a matter of time before the prevalence of TDR affecting this newest antiretroviral class reaches a level warranting baseline resistance testing for all patients entering care.

Integrate Inhibitors-Transmitted Drug Resistance Detected by UltraDeep Sequencing

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Among 92 patients analyzed with UDPS at baseline, 2 patients showed **R263K DTG** resistance mutation as minority quasispecie

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mutations detected by Sanger and by UDS</th>
<th>Mutations only detected by UDS %; mutational load (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>-</td>
<td>R263K 9,7%; 7099</td>
</tr>
<tr>
<td>15</td>
<td>L74I</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>L74I</td>
<td>R263K 13,5%; 8345</td>
</tr>
<tr>
<td>50</td>
<td>L74I</td>
<td>-</td>
</tr>
<tr>
<td>52</td>
<td>E157Q</td>
<td>-</td>
</tr>
<tr>
<td>59</td>
<td>L74I</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>E157Q</td>
<td>E138K 4,8%; 111</td>
</tr>
<tr>
<td>17123</td>
<td>L74I</td>
<td>-</td>
</tr>
</tbody>
</table>

Mutational load: viral load * percentage of the mutation detected by UDS
Clinical Case: ID 17310

- **Sex:** Male
- **Age:** 45 years
- **Risk Factor:** MSM
- **First HIV-1 seropositivity:** March 2016
- **CDC stage A3**
- **HIV-1 subtype:** F1
Clinical Case: ID 17310

On March 2016

**VL**: 92,000 copies/mL  **CD4**: 460 cells/µl

**GRT** (performed by both Sanger and NGS)

**PR**: L10V (100%) M36I (100%) L63A (100%) V77I (100%) L89M (99.9%)

**RT**: M184V (39.4%) M184M (60.6%)

**IN**: T97A (91.9%) N155H (38.8%) N155N (61.2%)

**Other pol mutations**

**PR**: K14R E35D R41K R57K Q61D H69Q I72V

**RT**: E6D K11R **M16V (2.5%)** V35T T39A K102R D123E I135V S162C K173T Q174R D177E I180V **E204K (1.4%)** Q207E R211K V245Q E248D A272P T286A E291D V292I I293V E297T I329L F346Y

**IN**: K14R S17T V37I M50I I72V A91T L101I **K103R (2.7%)** T112I S119R V165I V201I I220L Y227F L234V D256E **S283G (100%)**

**GP120/V3 (only sanger)**: I14M F20Y Y21W D29N Q32R H34Y

Tropism: Prevalence of a X4 tropic virus (FPR by Geno2Pheno: 3.8%)

- Figure 3, below, shows that although the prevalence of INI resistance is increasing, INI resistance remains low in comparison to RT and PI resistance.

* Persons with drug resistance mutations conferring a total score ≥30 (Stanford HIV Drug Resistance Algorithm v.7.0.1) to at least one INI, RT or PI.
Resistance to anti-HIV drugs is no longer a major problem in developed countries

- We cared about that…. But it is still with us.

- Without care, the problem will reappear

- For some geographic areas of Europe, ….still a relevant issue of major clinical importance
CONCLUSIONS

The new frontiers of resistance may be different than those we dealt with in the past
- The need of life-time success makes crucial the achievement of full control of virus replication, and at the same time of sparing future therapeutic options

- The usage/sequencing of antiviral classes may be different than in the past
  - NRTI backbone or new backbones?
    - Induction-maintenance?

- Where and how should we position the new antivirals/antiviral classes?
CONCLUSIONS

Achieving levels of undetectable virus is relatively easy, and does not require major diagnostic efforts.

Maintaining it for decades is a tough endeavour.
- A proper usage of antivirals, driven by a correct choice of antiviral therapies tailored on patient characteristics, remains a key medical need, for now and the future.