Il valore fondamentale delle resistenze nel guidare la terapia antiretrovirale

TERAPIA ANTIRETROVIRALE: UPDATE 2024

Lunedì 24 Giugno 2024 – Ore 16.00-19.00

24 giugno 2024

Nicola Gianotti

Potential conflicts of interest

OSPEDALE SAN RAFFAELE

Nicola Gianotti has been an advisor for Gilead Sciences, Janssen-Cilag, ViiV Healthcare and Merck Sharp & Dohme and has received speakers' honoraria from Gilead Sciences, ViiV Healthcare, Janssen-Cilag and Merck Sharp & Dohme.

A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy

John D. Baxter, Douglas L. Mayers[a], Deborah N. Wentworth[b], James D. Neaton[b], Marie L. Hoover[c], Mark A. Winters[d], Sharon B. Mannheimer[e], Melanie A. Thompson[f], Donald I. Abrams[g], Barbara J. Brizz[h], John P.A. Ioannidis[i], Thomas C. Merigan[d] and the CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)

Objective: To determine the short-term effects of using genotypic antiretroviral resistance testing (GART) with expert advice in the management of patients failing on a protease inhibitor and two nucleoside reverse transcriptase inhi

Design: Prospective randomized controlled trial.

Setting: Multicenter community-based clinical trials network.

Patients: One-hundred and fifty-three HIV-infected adults with rise in plasma HIV-1 RNA on at least 16 weeks of combination ar

Interventions: Randomization was either to a GART group, whe tation and suggested regimens were provided to clinicians, or where treatment choices were made without such input.

Main outcomes measures: Plasma HIV-1 RNA levels and CI measured at 4, 8, and 12 weeks following randomization. The change in HIV-1 RNA levels from baseline to the average of the 4

Results: The average baseline CD4 cell count was 230×10^6 c HIV-1 RNA was 28 085 copies/ml. At entry, 82 patients were containing indinavir, 51 on nelfinavir, 11 on ritonavir, and nine

Correva l'anno 2000 …
Quando tutto cominciò

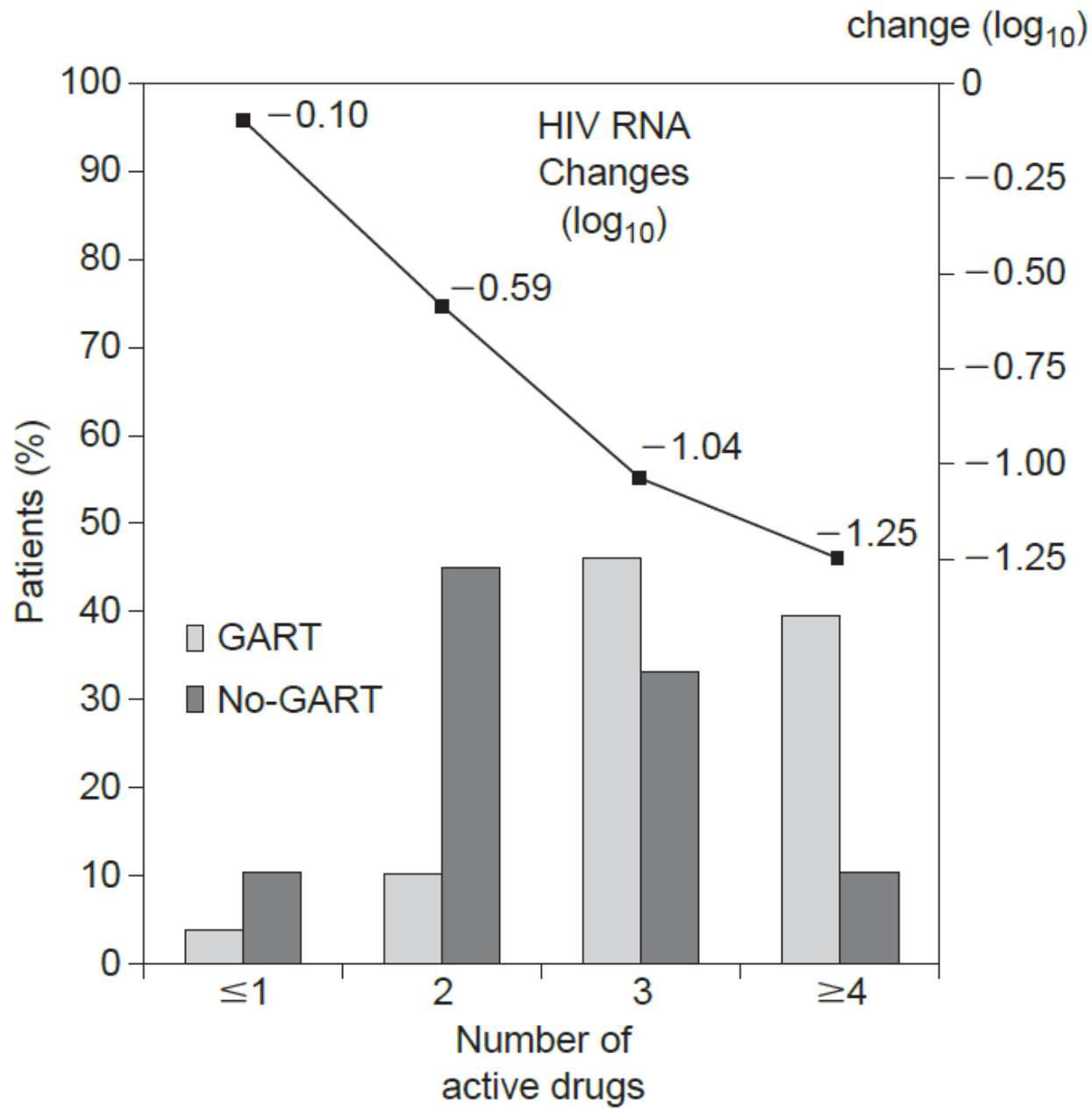
AIDS 2000, Vol 14 No 9

RNA, averaged at 4 and 8 weeks, decreased by 1.19 $\log_{10}$ for the 78 GART patients and -0.61 $\log_{10}$ for the 75 no-GART patients (treatment difference: −0.53 log, 95% confidence interval, −0.77 to −0.29; $P = 0.00001$). Overall, the best virologic responses occurred in patients who received three or more drugs to which their HIV-1 appeared to be susceptible.

Conclusion: In patients failing triple drug therapy, GART with expert advice was superior to no-GART as measured by short-term viral load responses.

AIDS 2000, **14**:F83–F93

Keywords: antiretroviral therapy, HIV drug resistance/resistance mutations, viral load


change (log_{10})
100
90
80
70
60
50
40
30
20
10
0
Patients (%)
0
−0.25
−0.50
−0.75
−1.00
−1.25
−0.10
−0.59
−1.04
−1.25
HIV RNA Changes (log_{10})
GART
No-GART
≤1
2
3
≥4
Number of active drugs

Attualità

- Cosa resta?

- Prospettive future

Ruolo test di resistenza nel 2024

- HTE
- Naïve
  - Anche in previsione di eventuali regimi successive a bassa barriera genetica
  - In PrEP users
- Long-acting
- GRT su DNA periferico

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International Journal of Infectious Diseases

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Heavily treatment-experienced persons living with HIV currently in care in Italy: characteristics, risk factors, and therapeutic options—the ICONA Foundation cohort study

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ABSTRACT

Objectives: Heavily treatment-experienced (HTE) people living with HIV (PLWH) pose unique challenges due to limited antiretroviral treatment (ART) options. Our study aimed to investigate the prevalence and features of HTE individuals followed up in the Italian Cohort Naïve Antiretrovirals (ICONA) cohort as of December 31, 2021.

Methods: HTE were defined based on meeting specific conditions concerning their current ART and their ART history up to December 31, 2021. Descriptive statistics were performed by HTE status. Regression analyses explored factors associated with becoming HTE based on pre-ART patients' characteristics. Cluster dendrogram analysis provided insights into subgroups with inadequate responses based on clusters of differentiation (CD4) counts and viral load (VL) trajectories.

Results: Among the 8758 PLWH actively followed in our cohort, 163 individuals (1.9%), mainly female, younger, Italian, and infected through heterosexual contact, met the HTE criteria. A lower CD4 count at ART initiation (odds ratio [OR] 1.60 per 100 cells/mmc lower CD4, 95% confidence interval [CI] 1.06-2.41, $P = 0.03$) and hepatitis C virus antibody positivity (OR 1.90, 95% CI 1.16-3.11, $P = 0.01$) were associated with higher HTE risk. Thirty PLWH exhibited ongoing immune-virological failure (18% of the HTE subgroup and 0.003% of the total population). Thirty PLWH exhibited ongoing immune-virological failure (i.e., with a current CD4 count <200 cells/mmc or VL>200 copies/mL). A cluster analysis identified 13 (43%) with a current CD4 count <200 cells/mmc. Also, notably, 19/30 (63%) had major acquired resistance-associated mutations to at least one antiretroviral drug class.

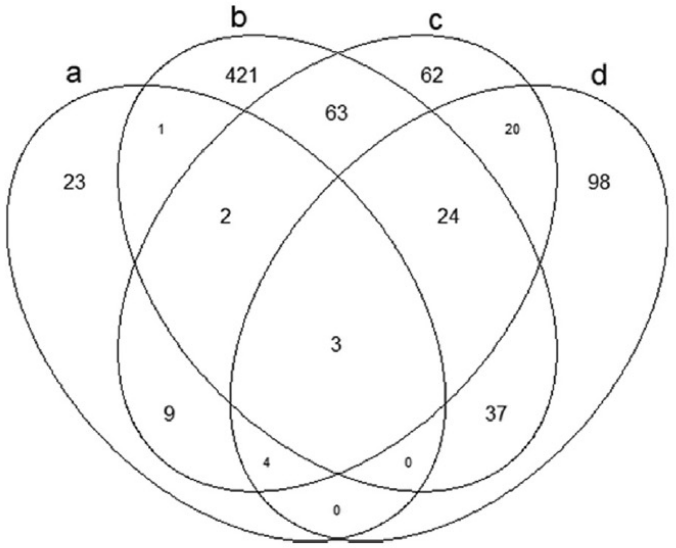

Figure 1. Venn diagram of the four definitions used to identify HTE subjects: (a) current regimen indicative of HTE; (b) at least three core ARV classes prior to current regimen; (c) individuals who had at least four anchor drug switches at any previous time; (d) ≥ three virological failures followed by a treatment switch.
ARV: antiretrovirals; HTE: heavily treatment-experienced.

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Conclusion

Despite limitations, our analysis enhances understanding of HTE patients. Modern antiretrovirals have reduced the impact on a small subset of patients with long treatment histories. Yet, within this group, roughly one-tenth face challenges, despite undetectable viral loads, with compromised immune status, increasing morbidity and mortality risk. Identifying suitable candidates for advanced treatments is crucial, holding the potential to extend life expectancy and improve the quality of life for most PLWHs.

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Journal of Antimicrobial Chemotherapy

Susceptibility of global HIV-1 clinical isolates to fostemsavir using the PhenoSense® Entry assay

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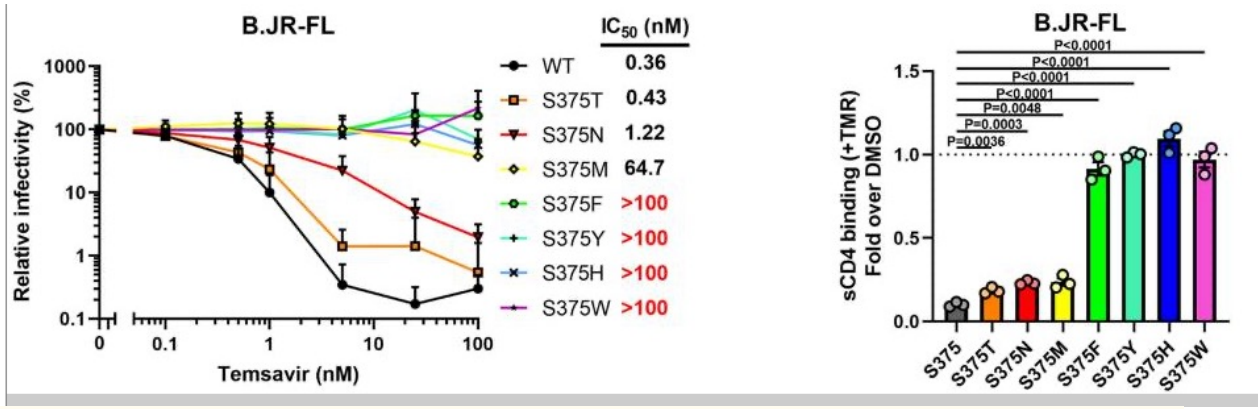
Background: Fostemsavir is a prodrug of a first-in-class HIV-1 attachment inhibitor, temsavir, that binds to gp120 and blocks attachment to the host-cell CD4 receptor, preventing entry and infection of the target cell. Previous studies using a limited number of clinical isolates showed that there was intrinsic variability in their susceptibility to temsavir.

Objectives: Here, an analysis was performed using all clinical isolates analysed in the Monogram Biosciences PhenoSense® Entry assay as part of the development programme.

Methods: In total, 1337 individual envelopes encompassing 20 different HIV-1 subtypes were examined for their susceptibility to temsavir. However, only seven subtypes (B, C, F1, A, [B, F1], BF and A1) were present more than five times, with subtype B (881 isolates) and subtype C (156 isolates) having the largest numbers.

Results: As expected, variability in susceptibility was observed within all subtypes. However, for the great majority of these viruses, temsavir was highly potent, with most viruses exhibiting IC_{50}s <10 nM. One exception was CRF01_AE viruses, where all five isolates exhibited IC_{50}s >100 nM. For the 607 isolates where tropism data were available, geometric mean temsavir IC_{50} values were remarkably similar for CCR5-, CXCR4- and dual mixed-tropic envelopes from infected individuals.

Conclusions: These data show that HIV-1 viruses from most subtypes are highly susceptible to temsavir and that temsavir susceptibility is independent of tropism.



Intrinsic resistance of HIV-1 CRF01_AE strains to neutralization by attachment inhibitor temsavir.

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doi:10.1093/jac/dkab257

Journal of Antimicrobial Chemotherapy

Prevalence of gp160 polymorphisms known to be related to decreased susceptibility to temsavir in different subtypes of HIV-1 in the Los Alamos National Laboratory HIV Sequence Database

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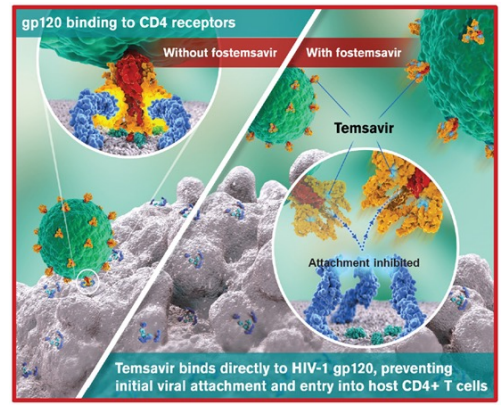
Background: Fostemsavir, a prodrug of the gp120-directed attachment inhibitor temsavir, is indicated for use in heavily treatment-experienced individuals with MDR HIV-1. Reduced susceptibility to temsavir in the clinic maps to discrete changes at amino acid positions in gp160: S375, M426, M434 and M475.

Objectives: To query the Los Alamos National Laboratory (LANL) HIV Sequence Database for the prevalence of polymorphisms at gp160 positions of interest.

Methods: Full-length gp160 sequences ($N = 7560$) were queried for amino acid polymorphisms relative to the subtype B consensus at positions of interest; frequencies were reported for all sequences and among subtypes/circulating recombinant forms (CRFs) with ≥10 isolates in the database.

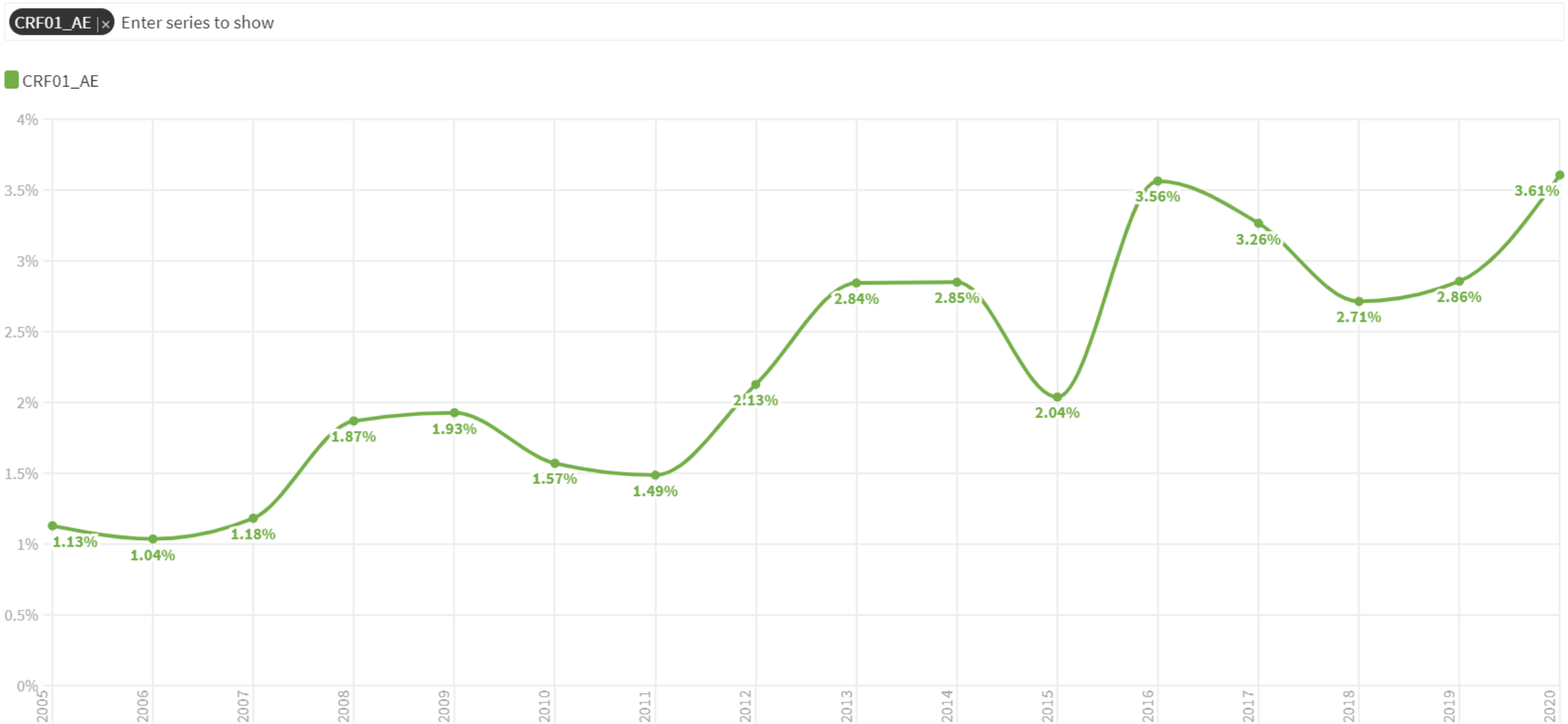
Results: Among 239 subtypes in the database, the 5 most prevalent were B ($n = 2651$, 35.1%), C ($n = 1626$, 21.5%), CRF01_AE ($n = 674$, 8.9%), A1 ($n = 273$, 3.6%) and CRF02_AG ($n = 199$, 2.6%). Among all 7560 sequences, the most prevalent amino acids at positions of interest (S375, 73.5%; M426, 82.1%; M434, 88.2%; M475, 89.9%) were the same as the subtype B consensus. Specific polymorphisms with the potential to decrease temsavir susceptibility (S375H/I/M/N/T/Y, M426L/P, M434I/K and M475I) were found in <10% of isolates of subtypes D, G, A6, BC, F1, CRF07_BC, CRF08_BC, 02A, CRF06_cpx, F2, 02G and 02B. S375H and M475I were predominant among CRF01_AE (S375H, 99.3%; M475I, 76.3%; consistent with previously reported low temsavir susceptibility of this CRF) and 01B (S375H, 71.7%; M475I, 49.5%).

Conclusions: Analysis of the LANL HIV Sequence Database found a low prevalence of gp160 amino acid polymorphisms with the potential to reduce temsavir susceptibility overall and among most of the common subtypes.



36. Most prevalent non-B subtypes and CRFs

Updated September 6, 2021 (ARCA - dbarca.net)



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ORIGINAL RESEARCH
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Trends of Transmitted and Acquired Drug Resistance in Europe From 1981 to 2019: A Comparison Between the Populations of Late Presenters and Non-late Presenters

Mafalda N. S. Miranda[1], Marta Pingarilho[1], Victor Pimentel[1], Maria do Rosário O. Martins[1], Rolf Kaiser[2], Carole Seguin-Devaux[3], Maurizio Zazzi[5], Francesca Incardona[6,7] and Ana B. Abecasis[1]*

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Background: The increased use of antiretroviral therapy (ART and morbidity of HIV-1 infected people but increasing level threatens the success of ART regimens. Conversely, late treatment outcomes, health costs, and potential transmission

Objective: To describe the patterns of transmitted drug resist drug resistance (ADR) in HIV-1 infected patients followed in patterns in late presenters (LP) vs non-late presenters (NLP), prevalent drug resistance mutations among HIV-1 subtypes.

Methods: Our study included clinical, socio-demographic, a from 26,973 HIV-1 infected patients from the EuResist Int between 1981 and 2019.

Results: Among the 26,973 HIV-1 infected patients in the were ART-naïve patients and 15,392 (57.1%) were ART-expe was 37 (IQR: 27.0–45.0) years old and 72.6% were males route was through heterosexual contact (34.9%) and 81.7% c Western Europe. 71.9% of patients were infected by subtype were classified as LP. The overall prevalence of TDR was overall decreasing trend (p for trend < 0.001), the ADR prevale a decreasing trend (p for trend < 0.001). For LP and NLP, 12.3 and 12.6%, respectively, while for ADR, 69.9 and 68.2 prevalent TDR drug resistance mutations, in both LP and NLP, T215FY, M184I/V, M41I/L, M46I/L, and L90M.

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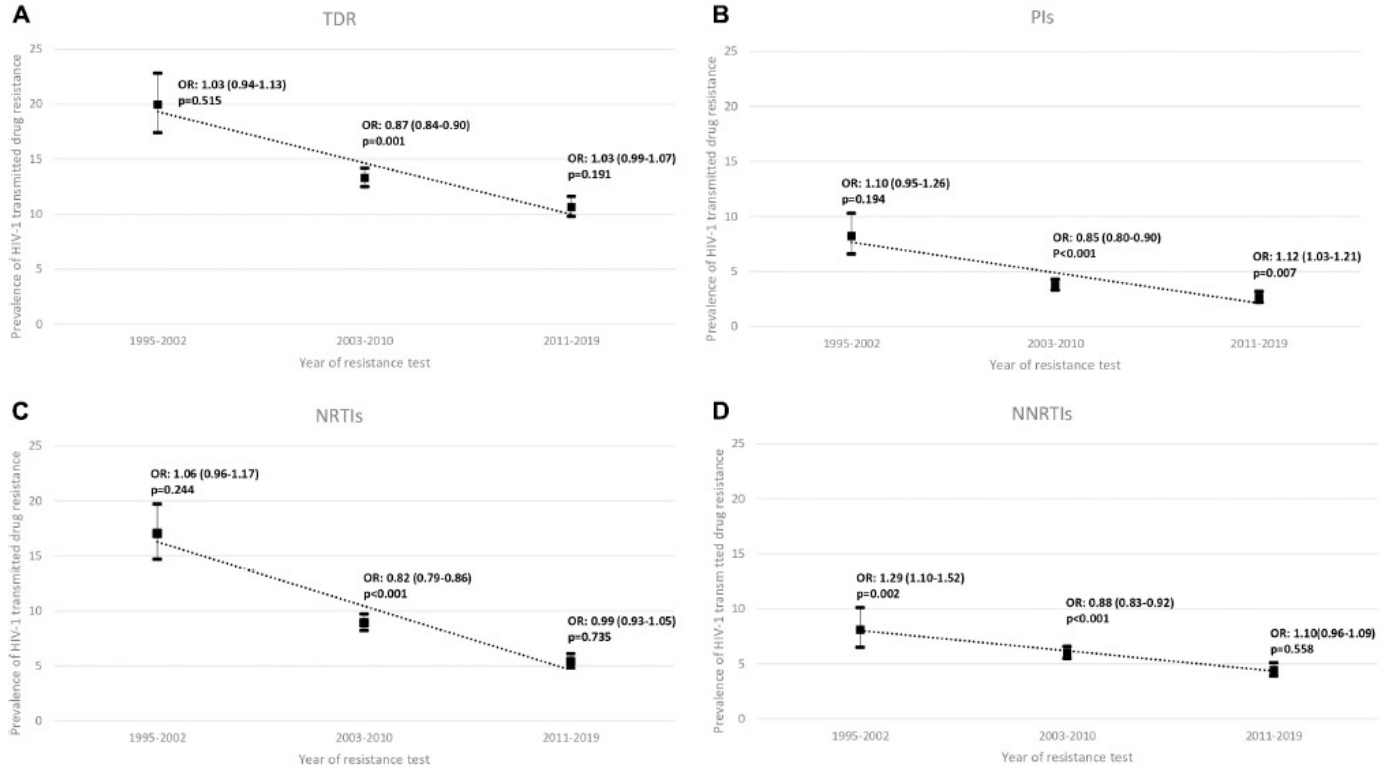

FIGURE 1 | Proportion of **(A)** overall transmitted drug resistance (TDR), **(B)** of protease inhibitors (PIs), **(C)** of nucleoside reverse transcriptase inhibitor (NRTIs) and **(D)** of non-nucleoside reverse transcriptase inhibitor (NNRTIs) in sequences from drug-naïve patients between three periods 1995–2002, 2003–2010, and 2011–2019. OR, Odds Ratio; p, p-value.

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Evaluation of HIV-1 integrase resistance emergence and evolution in patients treated with integrase inhibitors

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107 PWH InSTI-naive

Before INSTI treatment one patient harboured the major INSTI-RM R263K and three patients the accessory INSTI-RMs T97A.

These findings confirm that major INSTI-RMs very rarely occur in INSTI-naïve patients.

(4.7%). Concerning integrase evolution, a higher genetic distance was found in patients with ≥1 INSTI-RM compared with those without emergence of resistance (0.024 [0.012–0.036] vs. 0.015 [0.009–0.024], $P = 0.018$). This higher integrase evolution was significantly associated with a longer duration of HIV-1 infection, a higher number of past regimens and non-B subtypes.

Conclusions: These findings confirm that major INSTI-RMs very rarely occur in INSTI-naïve patients. Under INSTI treatment, selection of drug-resistance follows the typical drug-resistance pathways; a higher evolution characterises integrase sequences developing drug-resistance compared with those without any resistance.

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AIDS Research and Therapy

RESEARCH Open Access

Low clinical impact of HIV drug resistance mutations in oral pre-exposure prophylaxis: a systematic review and meta-analysis

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Abstract

Introduction Despite the widespread use of pre-exposure prophylaxis (PrEP) in preventing human immunodeficiency virus (HIV) transmission, scant information on HIV drug resistance mutations (DRMs) has been gathered over the past decade. This review aimed to estimate the pooled prevalence of pre-exposure prophylaxis and its two-way impact on DRM.

Methods We systematically reviewed studies on DRM in pre-exposure prophylaxis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guidelines. PubMed, Cochrane, and SAGE databases were searched for English-language primary studies published between January 2001 and December 2023. The initial search was conducted on 9 August 2021 and was updated through 31 December 2023 to ensure the inclusion of the most recent findings. The registration number for this protocol review was CRD42022356061.

Results A total of 26,367 participants and 562 seroconversion cases across 12 studies were included in this review. The pooled prevalence estimate for all mutations was 6.47% (95% Confidence Interval-CI 3.65–9.93), while Tenofovir Disoproxil Fumarate/Emtricitabine-associated drug resistance mutation prevalence was 1.52% (95% CI 0.23–3.60) in the pre-exposure prophylaxis arm after enrolment. A subgroup analysis, based on the study population, showed the prevalence in the heterosexual and men who have sex with men (MSM) groups was 5.53% (95% CI 2.55–9.40) and 7.47% (95% CI 3.80–12.11), respectively. Notably, there was no significant difference in the incidence of DRM between the pre-exposure prophylaxis and placebo groups (log-OR = 0.99, 95% CI −0.20 to 2.18, I2 = 0%; p = 0.10).

Discussion Given the constrained prevalence of DRM, the World Health Organization (WHO) advocates the extensive adoption of pre-exposure prophylaxis. Our study demonstrated no increased risk of DRM with pre-exposure prophylaxis (p > 0.05), which is consistent with these settings. These findings align with the previous meta-analysis, which reported a 3.14-fold higher risk in the pre-exposure prophylaxis group than the placebo group, although the observed difference did not reach statistical significance (p = 0.21).

Conclusions Despite the low prevalence of DRM, pre-exposure prophylaxis did not significantly increase the risk of DRM compared to placebo. However, long-term observation is required to determine further disadvantages of extensive pre-exposure prophylaxis use.

PROSPERO Number: CRD42022356061.

Keywords Pre-exposure prophylaxis, Mutation, HIV, Drug resistance mutation, Tenofovir, Emtricitabine

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Clinical Infectious Diseases
MAJOR ARTICLE

Type 1 Human Immunodeficiency Virus (HIV-1) Incidence, Adherence, and Drug Resistance in Individuals Taking Daily Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 Pre-exposure Prophylaxis: Pooled Analysis From 72 Global Studies

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Background. Oral pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (F/TDF) has high efficacy against HIV-1 acquisition. Seventy-two prospective studies of daily oral F/TDF PrEP were conducted to evaluate HIV-1 incidence, drug resistance, adherence, and bone and renal safety in diverse settings.

Methods. HIV-1 incidence was calculated from incident HIV-1 diagnoses after PrEP initiation and within 60 days of discontinuation. Tenofovir concentrations in dried blood spots (DBS), drug resistance, and bone/renal safety indicators were evaluated in a subset of studies.

Results. Among 17 274 participants, there were 101 cases with new HIV-1 diagnosis (.77 per 100 person-years; 95% confidence interval [CI]: .63–.94). In 78 cases with resistance data, 18 (23%) had M184I or V, 1 (1.3%) had K65R, and 3 (3.8%) had both mutations. In 54 cases with tenofovir concentration data from DBS, 45 (83.3%), 2 (3.7%), 6 (11.1%), and 1 (1.9%) had average adherence of <2, 2–3, 4–6, and ≥7 doses/wk, respectively, and the corresponding incidence was 3.9 (95% CI: 2.9–5.3), .24 (.060–.95), .27 (.12–.60), and .054 (.008–.38) per 100 person-years. Adherence was low in younger participants, Hispanic/Latinx and Black participants, cisgender women, and transgender women. Bone and renal adverse event incidence rates were 0.69 and 11.8 per 100 person-years, respectively, consistent with previous reports.

Conclusions. Leveraging the largest pooled analysis of global PrEP studies to date, we demonstrate that F/TDF is safe and highly effective, even with less than daily dosing, in diverse clinical settings, geographies, populations, and routes of HIV-1 exposure.

Keywords. pre-exposure prophylaxis; HIV-1; emtricitabine; tenofovir disoproxil fumarate.

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AIDS Research and Therapy

RESEARCH Open Access

Low clinical impact of HIV drug resistance mutations in oral pre-exposure prophylaxis: a systematic review and meta-analysis

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Abstract

Introduction Despite the widespread use of pre-exposure prophylaxis (PrEP) in preventing human immunodeficiency virus (HIV) transmission, scant information on HIV drug resistance mutations (DRMs) has been gathered over the past decade. This review aimed to estimate the pooled prevalence of pre-exposure prophylaxis and its two-way impact on DRM.

Methods We systematically reviewed studies on DRM in pre-exposure prophylaxis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guidelines. PubMed, Cochrane, and SAGE databases were searched for English-language primary studies published between January 2001 and December 2023. The initial search was conducted on 9 August 2021 and was updated t
of the most recent findings. The registration number for this proto

Results A total of 26,367 participants and 562 seroconversion cas
The pooled prevalence estimate for all mutations was 6.47% (95%
Disoproxil Fumarate/Emtricitabine-associated drug resistance mut
in the pre-exposure prophylaxis arm after enrolment. A subgroup
the prevalence in the heterosexual and men who have sex with m
and 7.47% (95% CI 3.80–12.11), respectively. Notably, there was no
between the pre-exposure prophylaxis and placebo groups (log-C

Discussion Given the constrained prevalence of DRM, the World
sive adoption of pre-exposure prophylaxis. Our study demonstrate
prophylaxis ($p > 0.05$), which is consistent with these settings. Thes
analysis, which reported a 3.14-fold higher risk in the pre-exposure
although the observed difference did not reach statistical significa

Conclusions Despite the low prevalence of DRM, pre-exposure p
of DRM compared to placebo. However, long-term observation is
of extensive pre-exposure prophylaxis use.

PROSPERO Number: CRD42022356061.

Keywords Pre-exposure prophylaxis, Mutation, HIV, Drug resistance mutation, Tenofovir, Emtricitabine

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Clinical Infectious Diseases
MAJOR ARTICLE

Type 1 Human Immunodeficiency Virus (HIV-1) Incidence, Adherence, and Drug Resistance in Individuals Taking Daily Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 Pre-exposure Prophylaxis: Pooled Analysis From 72 Global Studies

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ricitabine/tenofovir disoproxil fumarate (F/TDF) has high f daily oral F/TDF PrEP were conducted to evaluate HIV-1 liverse settings.

-1 diagnoses after PrEP initiation and within 60 days of BS), drug resistance, and bone/renal safety indicators were

w HIV-1 diagnosis (.77 per 100 person-years; 95% confidence d M184I or V, 1 (1.3%) had K65R, and 3 (3.8%) had both mutations. In 54 cases with tenofovir concentration data from DBS, 45 (83.3%), 2 (3.7%), 6 (11.1%), and 1 (1.9%) had average adherence of <2, 2–3, 4–6, and ≥7 doses/wk, respectively, and the corresponding incidence was 3.9 (95% CI: 2.9–5.3), .24 (.060–.95), .27 (.12–.60), and .054 (.008–.38) per 100 person-years. Adherence was low in younger participants, Hispanic/Latinx and Black participants, cisgender women, and transgender women. Bone and renal adverse event incidence rates were 0.69 and 11.8 per 100 person-years, respectively, consistent with previous reports.

Conclusions. Leveraging the largest pooled analysis of global PrEP studies to date, we demonstrate that F/TDF is safe and highly effective, even with less than daily dosing, in diverse clinical settings, geographies, populations, and routes of HIV-1 exposure.

Keywords. pre-exposure prophylaxis; HIV-1; emtricitabine; tenofovir disoproxil fumarate.

Ma quando la PrEP sarà cabotegravir, sarà lo stesso?

Participants With Confirmed Virologic Failure (CVF)

Participants With CVF in the mITT-E Population									
Sex at birth, country	**Baseline BMI (kg/m^2)**	**HIV-1 subtype at baseline**	**Viral load at SVF/CVF (copies/mL)**	**RPV RAMs observed at baseline (proviral DNA)**	**INI RAMs observed at baseline (proviral DNA)**	**RPV RAMs observed at failure (viral RNA)**	**INI RAMs observed at failure (viral RNA)**	**Phenotypic resistance (fold-change) to RPV/CAB**	**SVF timepoint (month)**
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spain†	22.9	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United States	30.5	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

- Two (0.4%) participants receiving CAB + RPV LA in the mITT-E population, and one additional participant receiving CAB + RPV LA in the ITT-E population, met the CVF criterion through Month 12
  - Two of the participants had on-treatment RPV and/or INI RAMs (genotyping for third participant failed at baseline)
- No participants in the BIC/FTC/TAF arm met the CVF criterion through Month 12

*Prior to enrolling in the study, the participant received BIC/FTC/TAF, and after discontinuation re-suppressed on DRV/c/FTC/TAF during long-term follow-up. †Prior to enrolling in the study, the participant had received dolutegravir/lamivudine/abacavir and BIC/FTC/TAF; they re-suppressed on BIC/FTC/TAF and darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. The participant did not continue in the long-term follow-up phase. ‡Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site. §Participant had HIV-1 subtype C at Month 3. Baseline analysis failed.
DRV, darunavir; ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not available; RAM, resistance-associated mutation; SVF, suspected virologic failure.

VF under Long-acting @CSL

Participant	Year of HIV diagnosis	Subtype	Body mass index (kg/m²)	Pre CAB+RPV regimen	HIV RNA at virological failure	RPV at failure	STI at failure	Genotypic resistance testing at failure	Post CAB+RPV regimen	HIV RNA post CAB+RPV switch
1. Male, 50 years	2005	B	22.2	DTG/ABC/3TC	371 copies/mL 436 copies/mL	121.8 ng/mL	Gonococcal urethritis	**NNRTI (RNA)** E138A **NNRTI (DNA)** E138EA **INSTI (RNA)** E138EK, Q148R **INSTI (DNA)** Q148QR	DRV/c/F/TAF	<50 copies/mL after 4 weeks
2. Male, 41 years	2007	B	25.7	DTG/RPV	34300 copies/mL	170.5 ng/mL	Gonococcal urethritis	**NNRTI (RNA)** K101PQ, E138A **INSTI (RNA)** E138K, Q148R	DRV/c/F/TAF	<50 copies/mL after 32 weeks
3. Male, 56 years	2012	B	24.6	B/F/TAF	636 copies/mL 66500 copies/mL	50.5 ng/mL	Primary syphilis	**NNRTI (RNA)** K101E, E138A **NNRTI (DNA)** K101KE, E138EA **INSTI (RNA/DNA)** E157Q	DRV/c/F/TAF	<50 copies/mL after 20 weeks
4. Male, 57 years	2018	B	25.3	B/F/TAF	276 copies/mL 55 copies/mL	70.8 ng/mL	/	**WT** for NNRTIs and INSTIs	B/F/TAF	<50 copies/mL after 1 week

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Fare GRT su DNA a tutti i pz di cui non abbiamo storia completa prima di iniziare LA CAB/RPV?

- Potrebbe essere utile
  - >rischio VF con selezione di varianti doppiamente resistenti a InSTI + NNRTI in caso di resistenza occulta alla BL
- Al momento non considerato indispensabile
- Costo non trascurabile
- Doppio rischio in caso di esecuzione universale
  - Non vedere mutazioni che in realtà esistono
  - Individuare mutazioni clinicamente ininfluenti (negando così l'opzione LA a persone che invece potrebbero beneficiarne)

GRT su DNA

- Il DNA provirale intatto (replication competent) sarebbe l'unico in grado di fornire informazioni certe sulla presenza di mutazioni clinicamente rilevanti nel DNA
  - >90% HIV-DNA è difettivo (=non-replication competent)
- Non è detto che le mutazioni che si trovano mantengano impatto clinico (se fissate in DNA difettivo, probabilmente ininfluenti)
- È meno sensibile del GRT storico da plasma
  - Non tutte le mutazioni si "fissano" in DNA
- Mutazioni APOBEC (complesso enzimatico dell'ospite, di difesa nei confronti dei retrovirus, che induce iper-mutazione virale)
  - Mutazioni iper-indotte dal self (molto spesso letali per il virus), non dalla selezione farmacologica
  - Alcune mutazioni potrebbero comunque compromettere la risposta ad alcuni farmaci
  - Dovrebbero essere segnalate dai virologi
  - NGS
- Mancanza di vera validazione

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REVIEW

Genotypic Resistance Testing of HIV-1 DNA in Peripheral Blood Mononuclear Cells

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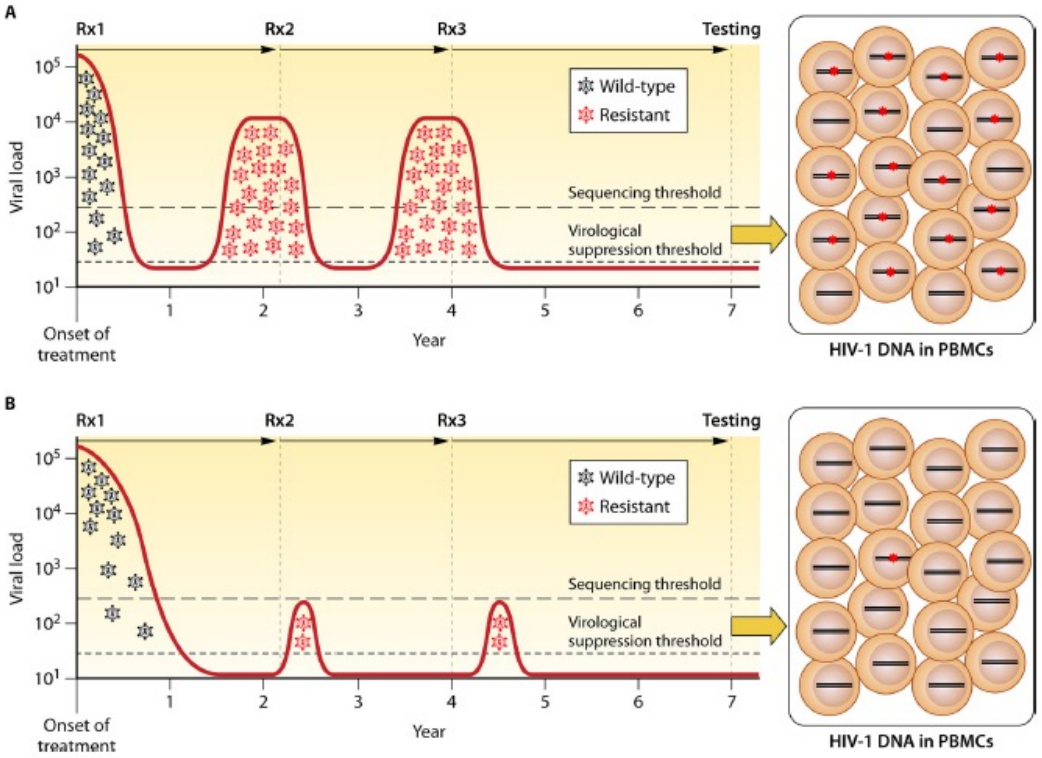

FIG 1 Sensitivity of peripheral blood mononuclear cell (PMBC) genotypic resistance testing (GRT) in patients with plasma virus suppression while receiving antiretroviral therapy (ART). In the first scenario (A), in which previous episodes of virological failure (VF) were prolonged and associated with high plasma HIV-1 RNA levels, the likelihood of detecting drug-resistance mutations (DRMs) in proviral DNA will be high. In the second scenario (B), in which previous episodes of VF were short and associated with low plasma HIV-1 RNA levels, the likelihood of detecting DRMs in proviral DNA will be low. Rx1, Rx2, and Rx3 followed by an arrow indicate periods of antiviral therapy. Proviral DNA containing DRMs are indicated by red asterisks in the boxes at the right side of the figure.

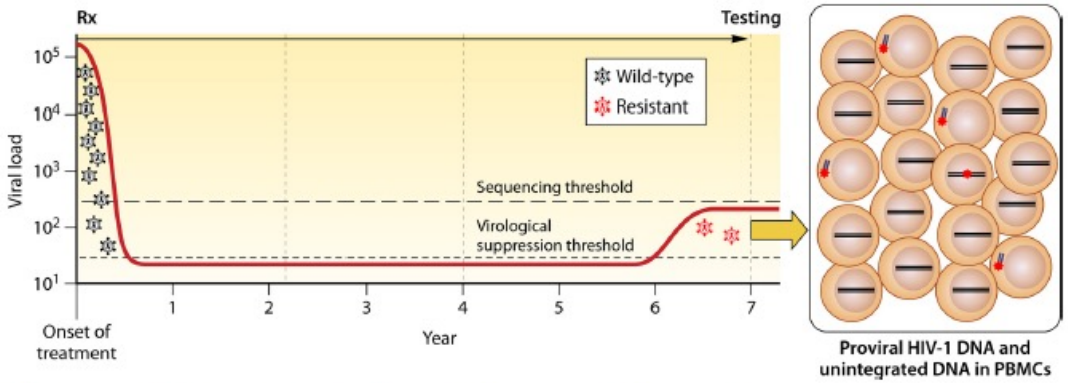

FIG 2 Sensitivity of PMBC GRT in patients with the recent development of low-level viremia while receiving ART. Rx followed by an arrow indicates the period of antiviral therapy. The dashed line indicates a threshold of between 200 and 500 copies/mL below which plasma virus GRT is often not successful. The likelihood of detecting DRMs in proviral DNA is likely to be low. Detecting DRMs in unintegrated linear and episomal viral DNA may be possible because these are more likely to reflect recently circulating viruses. Proviral and unintegrated viral DNA containing DRMs are indicated by red asterisks. In the boxed figure on the right, unintegrated linear viral DNA is shown outside the nucleus. Episomal DNA is not shown; its dynamics are likely to be closer to unintegrated linear DNA than proviral DNA.

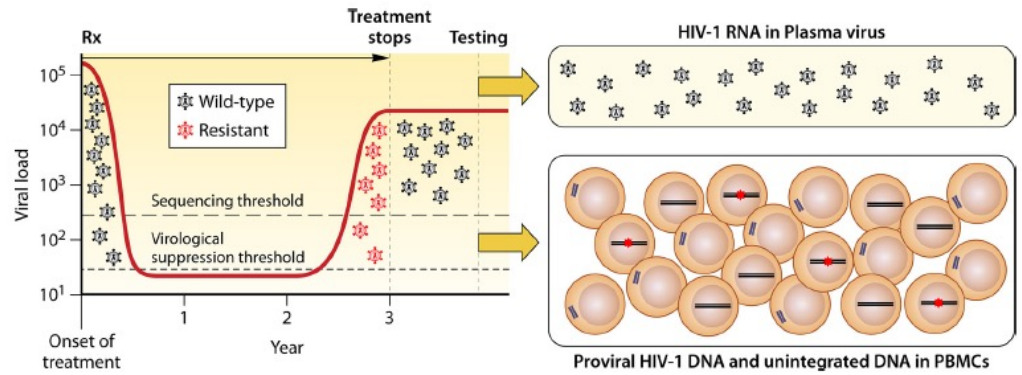

FIG 3 Sensitivity of plasma virus and PMBC GRT in patients who discontinue ART following VF and emergent HIV drug resistance (HIVDR). Rx followed by an arrow indicates the period of antiviral therapy. Most DRMs will no longer be detectable by plasma virus GRT within 2 to 3 months following ART discontinuation because plasma viruses containing DRMs are often rapidly outcompeted by ancestral wild-type viruses established in viral reservoirs prior to ART initiation. Although recently emergent DRMs may have begun to seed the proviral DNA reservoir, their levels in this compartment will be low unless VF has been prolonged. In addition, the presence of unintegrated linear and episomal viral DNA, which are in equilibrium with circulating plasma virus, may also reduce the proportion of viral DNA molecules containing DRMs. In the boxed figure on the right, proviral DNA containing DRMs are indicated by red asterisks. Unintegrated linear viral DNA is shown outside the nucleus. Episomal DNA is not shown; its dynamics are likely to be closer to unintegrated linear DNA than proviral DNA.

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen, see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions**, page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between Viral Hepatitis Drugs and ARVs
4. **Planned pregnancy or women wishing to conceive**, see Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

Principles

Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the viremia is suppressed it should not be assumed that the person is well adapted and tolerating the current regimen

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of comorbid conditions, and improve quality of life. The primary concern when switching should be to sustain and not to jeopardize virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures and historical resistance
2. The complete ARV history with HIV-VL, tolerability issue, cumulative genotypic resistance history and/or phases of viremia on previous regimens with the potential of resistance development should be evaluated prior to any drug switch
3. Switches within the same drug class (i.e. TDF/FTC -> TAF/FTC, EFV -> DOR or RPV) are usually virologically safe if equal potency and in the absence of resistance
4. Cross-class switches of single drugs with the same barrier to resistance (for example EFV to RAL) are usually virologically safe in the absence of resistance to the new compound
5. In case of prior virologic failures, with or without evidence of resistance, switches have to be planned especially carefully when they result in a lower barrier to resistance of the regimen. A PI/b may only be switched to an NNRTI, INSTIs RAL if full activity of the 2 NRTIs in the new regimen can be assumed based on resistance data, ARV history and HIV-VL results before switching (see 2.) Due to the higher barrier to resistance of DTG and BIC, it is currently unclear if a switch to DTG- or BIC-based regimens also requires full activity of 2 NRTIs in the combination
6. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. This requires knowledge about the resistance selection profile of the switch regimen. Especially, when reducing the number of drugs in a regimen or its barrier to resistance, the chances of composing a fully suppressive regimen after potential failure following switch should be considered
7. Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended
8. When selecting a new regimen, clinicians should carefully review the possibility of new drug-drug interactions with antiretroviral and concomitant medication leading to suboptimal drug exposure or toxicity, as well as the lag time for hepatic enzyme induction or blockade following discontinuation of the offending drug. Examples are: increased TDF toxicity with a PI/b or an increase in metformin exposure with DTG
9. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV and HBV vaccination status. TDF or TAF should not be discontinued in persons with chronic HBV
10. Persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity or tolerability issues of the new regimen
11. If someone receives and tolerates a regimen that is no longer a preferred option, and none of the other reasons for change applies, there is no need to change. Example: persons tolerating EFV-containing regimens
12. See online video lecture How to Change ART from the EACS online course Management of HIV and Co-infections

Dual therapies

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is
a) no historical resistance and
b) HBV immunity with anti-HBs antibodies (if non-immune provide HBV Vaccination, if isolated HBc antibodies see the section on Treatment and Monitoring of Persons with HBV/HIV Co-infection for details)

Oral dual therapies supported by large randomized clinical trials or meta-analyses:
DTG + RPV
XTC + DTG
XTC + DRV/b

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV and CAB + RPV

Long-acting intramuscular dual therapy CAB + RPV

- The use of oral lead-in (1 month) is optional
- Injections are administered every 2 months. In case of bridging, see the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

Initiation phase (start on day of last oral pills)	Continuation phase
Day 0: CAB 600 mg/ RPV 900 mg Month 1: CAB 600 mg/ RPV 900 mg	From month 2 onwards: CAB 600 mg/ RPV 900 mg every 2 months

The following baseline factors, when combined, are associated with risk of virologic failure and resistance:
- Archived RPV-associated mutations
- HIV subtype A6/A1
- BMI ≥ 30 kg/m²

See the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV for details, page 27

Strategies not recommended

a. Monotherapy
b. Dual or triple NRTIs combinations
c. Specific two-drug combination, i.e.1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, MVC + RAL, PI/b + MVC, ATV/b + RAL
d. Intermittent therapy, sequential or prolonged treatment interruptions.
In one open-label randomized study, 4 consecutive days a week of triple therapy was non inferior to 7 days a week, at 48 weeks in the context of close monitoring and counseling with visits every 3 months

2. The complete ARV history with HIV-VL, tolerability issue, cumulative genotypic resistance history and/or phases of viremia on previous regimens with the potential of resistance development should be evaluated prior to any drug switch

7. Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended

Conclusioni

- Il test di resistenza resta uno strumento fondamentale nella gestione della terapia antiretrovirale
- Per quanto i regimi di prima linea oggi utilizzati siano tutti ad alta barriera genetica, e per quanto la resistenza trasmessa a questi farmaci sia attualmente trascurabile, il GRT effettuato prima di iniziare la prima ART resta uno strumento essenziale per guidare strategie di semplificazione successive
  - La PrEP potrebbe in futuro cambiare in parte questo scenario.
- Il GRT su DNA va intepretato con MOLTA cautela e sempre alla luce della storia terapeutica