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Assessing the utilization of HIV genotype resistance testing: Insight from Italian Infectious Diseases Units

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ABSTRACT

Purpose: We aimed to assess the utilization of genotype resistance testing (GRT) by Infectious Diseases Units across Italy.

Methods: A cross-sectional study was conducted involving a questionnaire distributed to the Infectious Diseases Unit in Italy. A web-based survey using Google Forms software was utilized and spread via email or cellphone.

Results: Responses were obtained from 101 Infectious Diseases Units. Among these centres, only seven (6.9%) reported not performing GRT at any time. Of the 94 centres performing GRT, 52 (55.3%) sent blood samples to external laboratories. Notably, only 6/35 (17.1%) small centres had internal laboratories, compared to 14/35 (40.0%) medium centres and 22/24 (91.7%) large centres ($P < 0.001$). Most centres requested GRT for treatment-naïve individuals and all cases of virological failure. Only 24 (25.5%) requested GRT of HIVDNA before treatment changes. Regarding virological failure, most centres (38, 40.4%) requested GRT when HIV-RNA levels exceeded 200 copies/mL, while 26 (27.7%) requested it at levels exceeding 50 copies/mL. Additionally, 18 (19.1%) and 12 (12.8%) centres requested GRT at thresholds of 500 copies/mL and 1000 copies/mL, respectively. Regarding the specific GRT test used, 34 (36.2%) were unsure, while 16 (17.0%) reported using both next-generation sequencing and Sanger methods. Furthermore, 30 (31.9%) and 14 (14.9%) centres exclusively used next-generation sequencing and Sanger, respectively. Most centres reported receiving GRT results within 1 month ($n = 72$, 76.6%), while 22 (23.4%) centres obtained results within 2 weeks. However, 22 (23.4%) centres typically experienced more than 1-month delays. Finally, most participants (86, 91.5%) regarded GRT as a crucial routine test for the treatment of naïve people living with HIV.

Conclusions: This study demonstrates that most Infectious Diseases Units in Italy continue to consider GRT an essential test for newly diagnosed people living with HIV in clinical practice. However, the utilization of GRT on HIV-DNA remains limited. Further efforts are required to decrease turnaround time in centres experiencing prolonged delays in obtaining results.

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1. Introduction

As the global healthcare community continues to enhance HIV management strategies, the emergence of drug-resistant HIV strains presents a critical challenge, underscoring the importance of genotype resistance testing (GRT) in tailoring antiretroviral therapies (ART) [1–3].

Currently, two primary methods are available: Sanger sequencing and next-generation sequencing (NGS) [4]. The Sanger method, known as the chain termination method, is based on generating a single consensus sequence representing the dominant viral species, i.e., variants representing 20% of the entire viral population in the sample. For this reason, it provides only a small fraction of the resistance information as it is unable to detect minority mutations present at an intra-host frequency level <20% [5,6]. NGS, emerging in the early 21st century, represents a significant advance from traditional Sanger sequencing. It enables the simultaneous sequencing of millions of DNA fragments, providing a comprehensive genomic view. This technology is characterized by higher sensitivity that allows the detection of low abundance (<20%) viral variants [4]. Other advantages of NGS include improved time efficiency as well as the ability to analyse many samples simultaneously, reducing cost and labour compared with Sanger. Its versatility and efficiency have made NGS a cornerstone in modern genomic research and clinical diagnostics.

The COVID-19 pandemic, paradoxically, led to a surge in molecular diagnostics infrastructure and in parallel, enhanced HIV GRT capabilities. In the HIV field, the continued importance of GRT is recognized. Yet, its application varies widely across different healthcare settings due to factors like testing costs, resource availability, and regional healthcare policies. Internationally, guidelines on GRT differ and reflect diverse approaches to managing HIV [7–9]. For example, the World Health Organization (WHO) emphasizes a public health approach to HIV drug resistance surveillance, which generates data on resistance prevalence and patterns to guide national and global ART regimen decisions. In low- and middle-income countries, however, the WHO's 'Target Product Profile for HIV Drug Resistance Tests' outlines critical considerations for scaling up GRT, particularly in Africa. These include affordability, ease of use, and compatibility with limited-resource environments, highlighting the disparity in access to individualized patient management tools [10]

The necessity of GRT in treatment-naïve people living with HIV (PLWH) is still a topic of debate [11]. Factors involved include early and same-day ART initiation strategies, the relatively low prevalence of transmitted drug resistance, and the efficacy of modern ART regimens [12–14]. The development of ART regimens with higher genetic barriers, like second-generation integrase strand inhibitors, has reduced the risk of treatment failure due to resistance. However, recent studies and findings from Bavaro et al. [15] suggest minimal differences in virological suppression between naïve PLWH who started ART pending GRT results and those who started after receiving GRT results.

Current guidelines from the European AIDS Clinical Society recommend GRT prior to treatment initiation despite a lack of conclusive studies [7]. The WHO has not issued a formal recommendation for or against pretreatment GRT [8].

There is limited data in the literature about the frequency with which Infectious Diseases centres perform GRT and clinicians' perspectives on it. Therefore, our current study aims to assess the utilization of GRT across various Infectious Diseases Units in Italy.

2. Methods

The current study was conducted by the Antiviral Response Cohort Analysis group, a collective of researchers dedicated to monitoring HIV drug resistance and enhancing models for predicting virological response to antiretroviral therapy. While this study did not directly access the Antiviral Response Cohort Analysis database, it was inspired by the group's commitment to understanding and improving HIV treatment strategies in Italy.

In Italy, Infectious Disease Units play a pivotal role in HIV management. These units are distributed throughout the country and exhibit resource, capability, and patient demographics variations. Overall, there are 159 Infectious Disease Units, of which 59 (37.1%) are in the North of the country, 26 (24.5%) in the Centre, and 39 (38.4%) in the South.

The main objective of this study was to assess the utilization of GRT in various Infectious Disease Units across Italy. To do so, we performed a cross-sectional study, utilizing a web-based survey using Google Forms software, which was disseminated via email or cellphone to all Infectious Disease Units across Italy. We asked the person responsible for managing the HIV outpatient clinic in each Infectious Diseases Unit to respond.

The questionnaire aimed to collect information about the centre (number of PLWH followed, the availability of internal virological laboratory, etc.), information regarding the frequency and methods of GRT, the types of tests employed (Sanger or NGS), the turnaround time for test results, and clinicians' perceptions of the necessity and effectiveness of GRT, particularly in treatment-naïve patients. The English version of the questionnaire is available as Supplementary Material (S1).

We categorized centres based on the number of PLWH they serve: small centres are those with fewer than 500 PLWH; medium centres serve between 501 and 1000 PLWH; and large centres are defined as those serving more than 1000 PLWH.

2.1. Statistical analysis

Descriptive statistics were used to summarize the answers. Qualitative variables were summarized with absolute and relative (percentages) frequencies. Comparative analyses between different groups were conducted using chi-square tests or Fisher exact test for categorical variables, as appropriate. Statistical significance was set at a p-value of less than 0.05. All statistical analyses were performed with STATA version 16.1 (StatsCorp, TX, USA).

3. Results

The study elicited responses from 104 Infectious Diseases Units across Italy (Fig. 1).

Among these, a minority of 6 centres (5.8%) reported not performing GRT at any point (Table 1).

The majority, comprising 98 centres (94.2%), actively utilized GRT in their clinical practice, with 55 (56.1%) outsourcing blood

Table 1
Characteristics of 104 Italian infectious diseases centres.

Question	No of Infectious Disease Unit (104)
Size of centre	
≤300 PLWH	21 (20.2)
301–500 PLWH	18 (17.3)
501–1000 PLWH	41 (39.4)
≥1000 PLWH	24 (23.1)
Cohort study	
ARCA	33 (31.7)
ICONA	54 (51.9)
CISAI	14 (13.5)
VIRONET	15 (14.5)
None	33 (31.7)
Do you perform resistance test?	
Yes	97 (93.3)
No	7 (6.7)

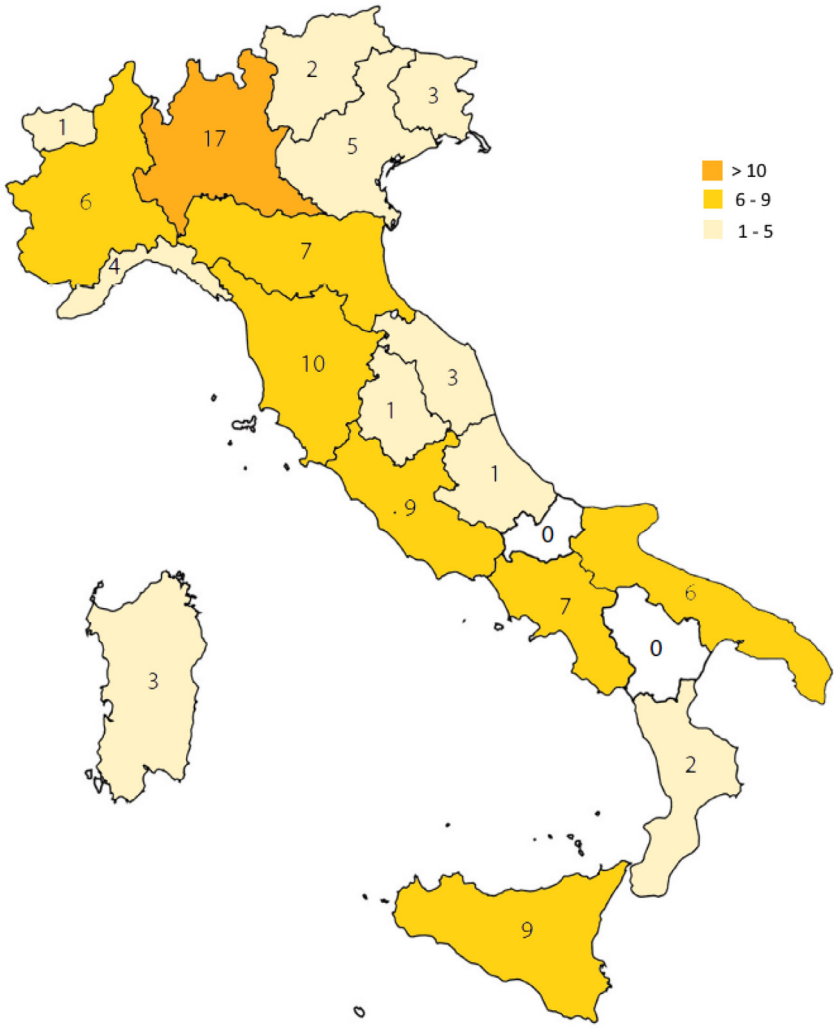

Fig. 1. Number of centres that replied to the questionnaire, divided by region.

sample analysis to external laboratories. A notable variance was observed based on the size of the centres: only 6 out of 39 small centres (15.4%) had the capability for internal laboratory GRT, in contrast to 15 of 41 medium centres (36.6%) and a significant 22 of 24 large centres (91.7%) ($P < 0.001$).

Regarding clinical practice, most centres, regardless of their size, reported requesting GRT for treatment-naïve individuals and in all cases of virological failure. A smaller proportion, 24 centres (24.5%), indicated that they requested GRT of HIV-DNA before treatment changes. The thresholds for virological failure prompting GRT varied: most centres (41, 41.8%) required GRT when HIV-RNA levels exceeded 200 copies/mL, while 26 centres (26.5%) did so at levels above 50 copies/mL. Lower numbers were observed at higher thresholds, with 19 centres (19.4%) requiring GRT at 500 copies/mL and 12 centres (12.3%) at 1000 copies/mL. Divergence was also seen in the specific methodologies used for GRT. A significant proportion of centres, 34 (34.7%), were uncertain of the specific method employed, whereas 17 centres (17.3%) reported using a combination of NGS and Sanger methods. Furthermore, 31 (31.6%) centres and 16 (16.3%) centres used exclusively NGS and Sanger method, respectively.

The turnaround time for GRT results varied across the centres. Most centres, 76 in total (77.6%), reported receiving results within 1 month. Within this group, 22 centres (23.5%) received results in less than 2 weeks. However, a notable proportion (22 centres [22.4%]), typically experienced delays exceeding 1 month.

The perception of the necessity of GRT in treatment-naïve PLWH was overwhelmingly positive, with 86 participants (87.8%) considering it a crucial routine test. The answers to the questionnaire are summarized in Table 2.

4. Discussion

This study, conducted across 101 Infectious Diseases Units in Italy, offers critical insights into the current practices and perspectives regarding GRT in HIV-1 management.

The preference for outsourcing GRT to external laboratories (55.3% of centres) may reflect resource limitations or strategic choices in smaller centres, as evidenced by larger centres' higher internal laboratory capabilities. This disparity raises questions about the uniformity of HIV-1 treatment across Italy, particularly in terms of turnaround time for test results and potential impact on treatment decisions.

The uncertainty among a significant portion of centres (36.2%) about the specific GRT methodology indicates a potential knowledge or communication gap within these units.

The fact that over half of the laboratories (52.1%) perform GRT on HIV-DNA not only testifies to the advancement in diagnostic capabilities but also significantly enhances the clinicians' ability to tailor ART. This approach is particularly beneficial in complex patient scenarios, such as those with low or undetectable viral loads. Having access to HIV-DNA resistance profiles allows for a more in-

Table 2
Detailed survey responses on GRT practices in 94 Italian Infectious Diseases Units.

Question	No (%) of Infectious Disease Unit
GRT performed in the same hospital	43 (43.9)
GRT performed in an external hospital	55 (56.1)
When do you request the GRT?	
Before ART start	93 (94.9)
At Virological failure	97 (100)
Before ART switch	24 (24.5)
Which part of the genome do you ask?	
I do not specify	40 (40.8)
PR/RT	54 (55.1)
INT	53 (54.1)
V3	6 (6.1)
GP41	4 (4.1)
Env	4 (4.1)
Gp120	3 (3.1)
Full length	4 (4.1)
Do you ask integrase test in naïve patients?	
Yes	90 (91.8)
No	8 (8.2)
Which methods have been used in your laboratory?	
Sanger	16 (16.3)
NGS	31 (31.6)
Both	17 (17.3)
I do not know	34 (34.7)
Does your laboratory perform GRT on HIV-DNA?	
Yes	50 (51.0)
No	39 (39.8)
I do not know	9 (9.2)
Does your laboratory give you information about the HIV subtype?	
Yes	78 (79.6)
No	18 (18.4)
I do not know	2 (2.0)
For which HIV-RNA do you ask GRT?	
>50 copies/mL	26 (26.5)
>200 copies/mL	41 (41.8)
>500 copies/mL	19 (19.4)
>1000 copies/mL	12 (12.3)
Do you send a synoptic for the GRT?	
Yes	64 (65.3)
No	26 (26.5)
Sometimes	8 (8.2)
Normally, how long do you have to wait for the GRT results?	
<2 weeks	23 (23.5)
2–4 weeks	53 (54.1)
>4 weeks	22 (22.4)
Do you think that the resistance test in naïve PLWH is crucial?	
Yes	86 (87.8)
No	12 (12.2)

env, envelope; GRT, genotypic resistance test; INT, integrase; NGS, next-generation sequencing; PLWH, people living with HIV; PR, protease; RT, reverse transcriptase.

formed and accurate simplification of therapy, ensuring that treatment regimens are optimized for individual patient needs. However, the results from GRT on HIV-DNA should be interpreted with caution. While HIV-DNA genotyping can reliably detect archived resistance mutations, it does not provide information about actively circulating viral variants. This distinction is particularly relevant in patients with low-level viremia, where plasma-based GRT offers critical insights into emerging drug resistance. Studies have demonstrated that HIV-1 genotyping of plasma samples can detect resistance mutations even at low viral loads (50–1000 copies/mL), making it predictive of virologic outcomes and a valuable tool for clinical decision-making [16,17]. By contrast, HIV-DNA genotyping focuses on archived resistance mutations within latent reservoirs, which may not always correlate with current resistance profiles. Although the absence of mutations in HIV-DNA does not guarantee their non-existence, detecting mutations is generally reliable [18]. Nevertheless, clinicians must recognize the limitations of HIV-DNA testing, particularly regarding its applicability in guiding ART modifications. This is especially crucial in the era of advanced treatment options, such as long-acting injectables and regimen simplification strategies, where accurate resistance profiles are paramount. The nuances of resistance detection across different compartments (plasma vs. DNA) highlight the importance of integrating comprehensive diagnostic data into personalized ART management.

The variability in thresholds for initiating GRT, ranging from >50 to >1000 copies/mL, could be a reflection of technical limitations in laboratories. Many laboratories may not be able to reliably identify mutations unless the viral load (VL) is sufficiently high. This could be due to different scenarios, including limited copy numbers, lower amplification success rates, and smaller plasma volumes. All these factors may render inaccurate genotyping results in samples with HIV-RNA <1000 copies/mL. This limitation can affect the timing of resistance detection, impacting the management of therapeutic interventions. Recognizing these technical constraints is crucial for understanding the variability in practice and underscores the need for continued advancements in diagnostic technology to support more uniform and effective HIV management.

Additionally, the variation in turnaround times for GRT results, with a notable 53.2% of centres waiting 2–4 weeks, underscores

a critical area for improvement in HIV care. A faster turnaround is crucial for timely clinical decisions, especially in managing virological failure or initiating treatment. Efforts to reduce these waiting times could significantly enhance patient care and treatment outcomes.

Despite the ongoing debate in the scientific community on the use of GRT, the vast majority of centres included in this study underline its importance in clinical practice. In fact, all centres perform GRT in case of virological failure, and 91.5% of centres also require it in treatment naïve PLWH.

The utility of GRT in individuals experiencing virological failure is unequivocally established; it is fundamental for guiding effective ART modifications. However, the role of GRT in treatment-naïve patients is more nuanced, especially considering the generally low levels of transmitted drug resistance. Nonetheless, there are compelling reasons to perform GRT in this group. Despite the relatively low prevalence of transmitted drug resistance, it remains consistently present and poses a potential risk to treatment success. The continuous monitoring and reporting of drug resistance data are critical for surveillance purposes, as they provide valuable insights into resistance trends and emerging mutations. These data not only inform public health policies but also guide the optimization of first-line ART regimens, ensuring their continued effectiveness. Moreover, as HIV infection is a chronic condition, characterizing the virus at the time of diagnosis is essential for understanding its potential evolution. Identifying resistance mutations early allows for better prediction of future virological outcomes and ensures that treatment strategies remain adaptable to the long-term management needs of PLWH. This approach underscores the importance of GRT not only for immediate clinical decision-making but also for its role in shaping long-term treatment outcomes and improving the overall quality of HIV care. In addition, a significant aspect of modern HIV management is the trend towards therapy simplification, including the transition to 2-drug regimens [7,19,20]. These regimens, such as the long-acting treatment with cabotegravir and rilpivirine, highlight the necessity of GRT in treatment-naïve individuals. Understanding the resistance profile before initiating such regimens is crucial to avoid functional monotherapy, where one of the drugs in a two-drug regimen becomes ineffective due to resistance mutations. This scenario could lead to treatment failure and the development of additional resistance mutations.

Moreover, it is vital to ensure the absence of pre-existing resistance for long-acting regimens, where the drugs remain in the body for extended periods. Orkin et al. [21] highlighted the increased risk of virologic failure in the presence of resistance mutations. This finding underscores the importance of conducting GRT before initiating such regimens. Knowing the resistance profile is essential to avoid functional monotherapy, where one drug in a two-drug regimen becomes ineffective due to existing resistance. This is particularly critical in long-acting regimens where drugs remain in the body for extended periods [22]. Moreover, the study's findings regarding the impact of HIV-1 subtypes and body mass index on the efficacy of these regimens further reinforce the necessity of GRT [21].

Therefore, GRT can inform clinicians about potential risks and guide them in selecting the most effective and safe treatment options, reducing the likelihood of regimen failure. For this reason, we strongly believe that, despite the low prevalence of transmitted resistance, GRT in treatment-naïve individuals remains a crucial step in personalized HIV care.

This study's limitations include its reliance on self-reported data, which may be subject to bias. Additionally, the responses may not fully capture the nuances of GRT practices in every Infectious Disease Unit in Italy, particularly those that did not participate in the survey.

In conclusion, our findings highlight the widespread use of GRT in Italian Infectious Disease Units, while also revealing significant variability in practices and perceptions. This study underscores the need for ongoing evaluation of GRT practices, especially in light of emerging ART regimens and evolving patterns of HIV drug resistance. We should further implement the research on the impact of these practices on patient outcomes and the cost-effectiveness of different GRT strategies.

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Ethical approval: This study did not require ethical approval as it solely involved a survey among healthcare professionals about their clinical practices and did not include patient participation or access to patient-specific data. The research was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The survey was anonymized to ensure the confidentiality and privacy of the respondents.

Declaration of competing interests: The authors declare not having conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2025.01.018.

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