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Demystifying the Athlete Biological Passport

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Introduction

Following a three-day hearing before the Court of Arbitration for Sport on 7-9 February 2024, the outcome of Simona Halep's appeal against her doping suspension is imminent and eagerly awaited. In September 2023, the former world number 1 tennis star was banned for four years by an independent tribunal for breaches of Article 2 of the Tennis Anti-Doping Programme ("**TADP**")[1], which broadly mirrors the WADA Code. The 2019 Wimbledon champion was held to have committed anti-doping rule violations ("**ADRVs**") in respect of two distinct (but inter-connected) charges:

- the presence of Roxadustat[2] (prohibited anti-anaemia medication) in a urine sample collected during the 2022 US Open; and
- the use of a prohibited substance and/or method during 2022 on account of irregularities in her Athlete Biological Passport ("**ABP**").

Aside from being one of the most high-profile sportspersons to be suspended for 'intentional' doping in recent memory, the first instance proceedings were notable for the number of experts deployed (four on each side, some of whom presented diametrically opposed opinions) and that the International Tennis Integrity Agency ("**ITIA**") had sought a six-year sanction on the basis that there were "Aggravating Circumstances"[3]. Ms Halep has vehemently maintained her innocence (blaming a contaminated collagen supplement called Keto MCT) but, aged 31, her career and reputation hang in the balance.

Compared to detecting a banned substance, evaluating an ABP is a more abstract and nuanced process. Whilst we await the CAS Award, I will be focussing on the decision of the first instance tribunal in *ITIA v Halep* SR/354/2022, which expressly noted that the ABP programme is "*complex in the underlying science, mathematics and statistics*"[4]. Whilst Halep's circumstances are slightly different, an athlete who has never tested positive for a banned substance could conceivably end up with a four-year ban for 'presence or use of a banned substance or method'. With so much at stake for Ms Halep and others, this article takes a closer look at what the ABP is, how the procedure works under the WADA regime, and how accurate/reliable a biological algorithm can be at (indirectly) determining ADRVs.

What is the ABP?

> "*The fundamental principle of the Athlete Biological Passport is to… reveal the effects of doping, rather than attempting to detect the doping substance or method itself.*" (WADA website)

The ABP is a method of monitoring samples over a period of time to locate and assess variations amongst specific biological markers that may indicate doping.[5] It was first implemented in 2008 by the International Cycling Union ("**UCI**"), in response to the existential blood doping crisis that gripped the sport, and many SGBs have since followed suit. Initially, the ABP exclusively concerned the 'Haematological Module' (using blood samples to monitor oxygen transportation) but now also includes a 'Steroidal Module' (since 2014, using urine to monitor natural steroid production in the body) and an 'Endocrine Module' (as of August 2023, to identify markers of growth hormone doping).

Each new sample is fed into the ABP which contains a digital record of an athlete's samples over time. A computerised algorithm then conducts a longitudinal evaluation of biomarkers against all the previous results and makes predictions for their ABP profile (or individual biological 'landscape'). If subsequent samples have markers that fall outside the athlete's normal/expected range, this will be flagged as 'abnormal' and warrants further examination/investigation (see below).

Longitudinal monitoring of biomarkers – how does it work?

When an athlete is first added to an ABP programme, his/her 'landscape' is based on differentiators such as gender, age, ethnicity and sports discipline but, as more samples are added, the model is adapted to adjust to the biological markers of the individual athlete ("**Adaptive Model**"). In other words, the athlete becomes their own point of reference, rather than the algorithm relying on generic norms that are not unique to an individual's own biology. In the case of Ms Halep, she provided 56 blood samples under the ABP programme between August 2013 and March 2023, of which 51 (valid samples) were taken into account as part of the recent proceedings.[6]

The types of parameters measured in blood samples would, for instance, include the concentration of haemoglobin ("**HGB**") and percentage of new red blood cells (reticulocytes or "**RET**"), which can be combined to produce a so-called OFF-score. The Adaptive Model uses the algorithm to assess the likelihood of each marker falling outside the predicted range that would typically be observed in a healthy, non-doping athlete. If that likelihood is less than 1 in 100 (or 1 in 1,000 for sequence variations), an 'Atypical Passport Finding' ("**APF**") is generated by the Adaptive Model in ADAMS.

The ABP evaluation procedure

Once an APF is flagged, this sets in motion a results management process in accordance with Annex C of WADA's International Standard for Results Management ("**ISRM**").[7] The automated evaluation (relying on software) switches to expert evaluation (by humans), who will determine whether the observed abnormality (i) is an extreme of natural variation (and can therefore be considered normal), (ii) is caused by pathology, (iii) is indicative of doping (but further testing is required); or (iv) bears clear features of doping (and does not require further testing).

It is worth noting that, even where there is no APF flagged on ADAMS, a WADA-approved Athlete Passport Management Unit ("**APMU**") may also refer an ABP for expert evaluation (for instance, where certain data falls outside the Adaptive Model, there is intelligence regarding the athlete in question, etc).[8]

The anonymised evaluation process is predicated on a two-layer system of experts[9]:

- Expert Evaluation (by initial expert): a first expert conducts an initial review and renders an evaluation – 'normal', 'suspicious', 'likely doping' or 'likely medical condition' – based on the information available at the time.
- Expert Evaluation (by initial expert + two additional experts)**:** if the first expert deems the ABP profile to be typical of doping, it is then subject to review by three experts (the initial expert and two further independent experts). As part of their evaluation, the experts may request additional information, such as the athlete's whereabouts and competition schedule.
- Athlete Explanation**:** if there is a consensus of 'likely doping' amongst all three experts, an APF is declared and the athlete will be contacted, provided with supporting documentation, and offered the opportunity to provide an explanation. As stated in the *Halep* decision, this is the first opportunity for the athlete to provide "*an appropriate physiological explanation or to bring up environmental factors or a medical condition*".[10]
- Expert Evaluation (Expert Panel): the explanations by the athlete are, again, anonymously evaluated by the expert panel, who will reassess their previous opinions in light of the explanation provided. Ms Halep, for example, had sought to argue that (i) her ABP was always within the normal range, and (ii) there were other confounding factors that innocently explained her blood values (e.g. blood loss during surgery, a period of detraining, etc).[11] Nevertheless, on the evidence before them, "*each of the three experts had a high degree of confidence that there was no innocent explanation*".[12]
- ADRV Charge: if the Expert Panel maintain their unanimous conclusion that use of a prohibited substance or method was 'highly likely', the athlete will be formally charged with an ADRV by the Passport Custodian (e.g. the ITIA). The burden of proof will be on the prosecuting body to the standard of 'comfortable satisfaction'[13] but, as made clear by the tribunal in *Halep*, "*a player who does not offer any cogent explanation is at serious risk of being held guilty as charged*."[14]

How effective is the ABP at catching dopers?

The ABP was born out of the difficulty of directly detecting blood doping (definition below) via blood or urine samples.

What is blood doping?
The illicit method of boosting athletic performance by increasing the number of red blood cells in the bloodstream (i.e. enabling the body to carry more oxygen to muscles).

Examples:

- Use of erythropoiesis-stimulating agents (e.g. rhEPO)
- Infusion of synthetic haemoglobin-based oxygen carriers (HBOCs) or perfluorocarbons (PFCs)
- Autologous blood transfusions (i.e. using blood obtained from self)
- Homologous blood transfusions (i.e. using blood obtained from compatible donors)

As regards erythropoietin ("**EPO**") – a hormone mainly produced in the liver and kidneys that stimulates the production of red blood cells in bone marrow – the synthetic version ("**rhEPO**") (i) is structurally very similar to the endogenous version,[15] and (ii) only remains in the body for a very short period of time.[16] Unsurprisingly, EPO was abused in a number of endurance sports, most rampantly in the 1990s and early 2000s. The introduction of the ABP was an example of anti-doping

authorities fighting back against these types of practices.

In the period 2008 to 2021, circa 500 athletes have reportedly been charged with ADRVs on the basis of passport data alone,[17] with over 180 sanctions issued.[18] The ABP can be used to directly sanction athletes pursuant to Article 2.2 ('use or attempted use by an athlete of prohibited substance or method'), as seen in *Halep*. The indirect impact can be harder to measure, but information gleaned from the ABP can be used as an investigative tool, such as to guide decision-making on:

- the targeted testing of certain athletes or groups of athletes with additional samples.
- conducting further analysis of existing samples by utilising alternative analytical methods – for instance, Isotope Ration Mass Spectrometry ("I**RMS**") analysis to differentiate between endogenous and exogenous steroids.
- the long-term storage of specific sample(s) for re-analysis in the future.

There are certain metrics that point to the indirect success of the ABP in tackling doping. For instance, since the introduction of the ABP(i) the number of 'traditional' anti-doping tests positive for EPO has increased by 300%, as highlighted in *Mottram and Chester*[19], and (ii) studies on cyclists have also shown a sharp decline in the RET percentage (which is a marker for blood doping).[20] The reason for the latter may be due to the deterrent effect of the ABP, as athletes will be acutely aware that all data will remain on their passport for their entire career, even if a one-off borderline result is not sufficient to constitute an adverse analytical finding ("**AAF**").

Criticisms of the ABP

Whilst many stakeholders believe ABP has been a positive instrument in the fight against doping, particularly as regards EPO use, not all are convinced as to its efficacy in catching cheaters. Criticism (or caution) as to the effectiveness of the ABP has included the following:

- Frequency of testing: the discrepancy in the number of tests can be stark between different athletes and sports. The ABP is reliant on long-term trends so, without data (and lots of it), the statistical accuracy is blunted.
- Micro-dosing: according to a study published in February 2023, "*in order to reduce the detection window for blood doping, athletes have been applying low doses of rhEPO (e.g., <10 IU/kg body weight, daily or every second day) instead of larger doses twice or more per week (e.g., 30 IU/kg)*."[21] Meanwhile, other experts have suggested that micro-doping at 11pm can leave no anti-doping markers by 6am the following morning, hence it can be exploited by doping athletes.[22]
- Plasma volume: certain blood parameters used in the ABP are purportedly influenced by the plasma volume of the blood (principally water, but also some dissolved proteins, glucose and hormones). There are various 'legal' factors that affect plasma volume, such as heat, illness, training load and altitude. Carsten Lundby, who conducted a 2012 study on altitude training in elite athletes[23], has warned: "*if you want to cheat, go to high altitude and explain your blood transfusion results as altitude training… it's what ABP is not a perfect system*."[24]
- Access to personal data: currently, athletes are able to access their haematological (but not steroidal) data from the ABP for data privacy reasons.[25] This has led to criticisms that allowing athletes access to their raw data, such that they can monitor their parameters, may jeopardise the very purpose of the programme.[26] Indeed, in a 2018 journal publication by *Devriendt et al* on this issue, the authors argued that "*safeguarding the integrity of the ABP system must be seen as the most essential element and thus a departure from immediate data disclosure is necessary*."[27]

- Subjectivity of human analysis: unlike traditional testing procedures, where the simple presence of a substance or its metabolites determines whether there is an AAF, the ABP process requires expert evaluation (as outlined above). Although the two-tier evaluative process builds in certain checks and balances, the subjective component for determining an APF means that human error can therefore be inevitable in certain instances – in terms of both false positives and dopers slipping through the net.

Conclusion and the future

Scientific developments cut both ways. On one hand, there are increasingly sophisticated doping techniques being deployed, and on the other, more and more advanced detection systems. It can be rather chicken or egg in that respect but, overall, the data suggests that the ABP programme has proved an effective tool in fighting doping. The fact that WADA stipulates that all endurance sports must have an ABP programme in place for their top-level athletes is, or appears to be, testament to that.[28]

However, as some of the criticisms highlighted above suggest, the ABP is far from being a silver bullet in the war on doping. The ABP is largely confined to elite athletes and blood testing, on which the programme relies, and is more expensive and practically complicated than urine samples.[29] It might therefore be considered just one part of the overall anti-doping jigsaw.

The ABP is here to stay, but not necessarily in its current form. We have recently seen the introduction of the Endocrine Module (as mentioned above) and ingenuity and innovation look set to continue. A 2022 study titled ‘Future opportunities for the ABP’[30] suggested that machine-based learning approaches are inevitable for aiding expert interpretation, as well as ‘omics’ strategies to search for new biomarkers and the use of artificial intelligence (**“AI”**). Regarding the latter, AI has moved from a buzzword to something mainstream. With WADA prepared to invest in AI-related research projects[31], provided sufficient funding is in place, one would expect this to play an increasingly prominent role in anti-doping detection.

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[1] The provisions of the TADP broadly mirror those in the WADA Code.

[2] Roxadustat, also known as FG-4592, is prohibited in a sporting context because it increases haemoglobin and the production of red blood cells.

[3] For instance, due to the apparent repetitive, sophisticated and deceptive nature of Ms Halep’s actions, the timing of erythropoietic suppression around major events, etc. See *ITIA v Simona Halep*, SR/354/2022, para. 369

[4] *ITIA v Simona Halep*, SR/354/2022, para. 242

[5] April Henning and P Dimeo, *Doping – A Sporting History*, (London: Reaktion Books, 2022), p.176

[6] *ITIA v Simona Halep*, SR/354/2022, paras. 255 and 337

[7] Also set out in Section 3.7 of WADA’s ABP Operating Guidelines

[8] See Section C.2.2.4 of the ISRM

[9] *ITIA v Simona Halep*, SR/354/2022, paras. 242-287

[10] *ITIA v Simona Halep*, SR/354/2022, para. 277

[11] *ITIA v Simona Halep*, SR/354/2022, paras. 304-325

[12] *ITIA v Simona Halep*, SR/354/2022, para. 361

[13] The 'comfortable satisfaction' test (greater than balance of probability but less than proof beyond reasonable doubt) has been applied for many years by the CAS and other sports disciplinary tribunals. In the context of ABP charges, in *Ivanov v RUSASA*, CAS 2019/A/6254 (at para 145), the sole arbitrator equated the experts' evaluation 'highly likely' doping with the standard of 'comfortable satisfaction'.

[14] *ITIA v Simona Halep*, SR/354/2022, para. 277

[15] Jules Heuberger, Peter van Eenoo et al, '*Sensitivity and specificity of detection methods for erythropoietin doping in cyclists*', Drug Test Anal. 2019 Sep;11(9):1290-1301. doi: 10.1002/dta.2665. Epub 2019 Jul 17. PMID: 31232530; PMCID: PMC6790592.

[16] Aside from the urine test for rhEPO being very expensive, it only detects rhEPO administered a few hours or days prior to sample collection.

[17] David Mottram and Neil Chester, *Drugs in Sport* (8th Edition: Routledge, 2022), p.98

[18] 'WADA's Athlete Biological Passport; an important tool for protecting clean sport' (WADA website, 19 August 2021): https://www.wada-ama.org/en/news/wadas-athlete-biological-passport-important-tool-protecting-clean-sport

[19] David Mottram and Neil Chester, *Drugs in Sport* (8th Edition: Routledge, 2022), p.98

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[24]James Witts, '*Biological Passport: Have dopers found ways to beat it?*' (Cycling News, 17 July 2020) https://www.cyclingnews.com/features/biological-passport-have-dopers-found-ways-to-beat-it/

[25] Devriendt T, Chokoshvili D et al. '*Do athletes have a right to access data in their Athlete Biological Passport?*' Drug Test Anal. 2018 May;10(5):802-806. doi: 10.1002/dta.2380. Epub 2018 Apr 20. PMID: 29524351. https://pubmed.ncbi.nlm.nih.gov/29524351/

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[28] David Mottram and Neil Chester, *Drugs in Sport* (8th Edition: Routledge, 2022), p.98

[29] *ITIA v Simona Halep*, SR/354/2022, para. 352

[30] Krumm B, Botrè F, Saugy JJ and Faiss R. '*Future opportunities for the Athlete Biological Passport. Frontiers in Sports and Active Living*'. 2022 ;4:986875. DOI: 10.3389/fspor.2022.986875. PMID: 36406774; PMCID: PMC9666424. https://www.frontiersin.org/articles/10.3389/fspor.2022.986875/full

[31] https://www.wada-ama.org/en/news/wada-renews-partnership-fonds-de-recherche-du-quebec

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