The game begins with one of three lifepaths for the player character V: Nomad, Streetkid, or Corpo. Each lifepath ultimately involves V partnering with street thug Jackie Welles. The two begin working as mercenaries in Night City along with netrunner, T-Bug. In 2077, Dex hires V and Jackie to steal a biochip known as "the Relic" from Arasaka Corporation. They acquire the Relic, but the plan goes awry when they witness the murder of the megacorp's leader Saburo Arasaka at the hands of his son Yorinobu. Yorinobu covers up the murder as a poisoning and triggers a security sweep, in which T-Bug is killed. V and Jackie escape, but Jackie is fatally wounded in the process while the Relic's protective case is damaged, forcing V to insert the biochip into their head. Furious at the unwanted attention, Dex shoots V in the head and leaves them for dead in a landfill. Upon awakening, V is haunted by the digital ghost of war veteran turned iconic rock star and terrorist Johnny Silverhand, believed to have died in 2023 during his own thermonuclear attack on Arasaka Tower. V is then rescued by Saburo's bodyguard Goro Takemura on Arasaka's orders, as they are the prime suspect in Saburo's death, but the duo are attacked by Arasaka assassins sent by Yorinobu. They fend off the attackers and reach V's ripperdoc Viktor Vector, who reveals that resurrection nanotech on the biochip saved V's life, but also started an irreversible process that would overwrite V's consciousness with Johnny's, whose memory engram is stored on the chip. V has only a few weeks before the process completes, and the biochip cannot be removed without instantly killing V, so V must find a way to remove Johnny and survive. Inferring from the assassins that V is innocent of Saburo's murder, Takemura and V start working together. From here, V follows up on two different leads: tracking down Arasaka's head doctor Anders Hellman, which V accomplishes by working with Panam Palmer, a member of the Aldecaldos nomad clan; and finding and rescuing Evelyn Parker, Dex's client who commissioned the gig. After capturing Anders, V attempts to contact Evelyn Parker for help, only to learn that she was kidnapped by a gang. With the help of Evelyn's friend Judy Álvarez, they are able to save her, but Evelyn is in a near-death state. By viewing Evelyn's memories through a braindance, V gets in contact with the Voodoo Boys, a gang of netrunners. Evelyn later commits suicide as a result of psychological trauma stemming from her being raped while kidnapped. Through the Voodoo Boys, V relives Johnny's memories, learning that in 2013, Johnny's thengirlfriend Alt Cunningham created Soulkiller, an artificial intelligence able to copy netrunners' minds through their neural links, but destroyed the target's brain in the process. Arasaka kidnapped Alt and forced her to create their own version of Soulkiller, which would store the minds of its targets in Arasaka's digital fortress, Mikoshi. With the help of his friend Rogue Amendiares, Johnny led a rescue effort to save Alt, but failed to find her before Arasaka used Soulkiller on her; Johnny's later thermonuclear attack was a cover to free Alt's consciousness from Arasaka's subnet, but Arasaka's head of security Adam Smasher captured him and used Soulkiller on him as well. By 2077, Arasaka was advertising a "Secure Your Soul" program and conducting secret research into writing a digital copy of a mind into a living human brain, from which the Relic arose. V also gets in contact with Alt's consciousness, which has escaped beyond the Blackwall, a firewall which protects the net from rogue Als. With Johnny's mediation, V makes a deal with Alt, that if they can give Alt access to Arasaka's subnet and gain physical access to Mikoshi, Alt can use Soulkiller to separate V's and Johnny's consciousness. Working with Takemura, V helps him capture Yorinobu's sister, Hanako Arasaka, to convince her of Yorinobu's treachery. After defeating Takemura's former student Oda, they escort Hanako to a safe house and convince her of V's innocence, but V is forced to flee when Arasaka soldiers close in. Eventually, V must decide whether to mount an attack on Arasaka Tower to gain physical access to Mikoshi and use Soulkiller to remove Johnny from their body, or to make a deal with Hanako to extract the Relic. If V chooses to attack Arasaka Tower, depending upon player actions throughout the game, V can choose different options to conduct the attack. V

can allow Johnny to take over and stage the attack with Rogue, suppress Johnny and mount the attack with their nomad allies from the Aldecaldos clan, mount the attack solo, or simply commit suicide. All options (except for the suicide one) end with V defeating Adam Smasher. If V chooses to make a deal with Hanako instead, they convince the Arasaka board that Yorinobu killed Saburo, and oust Yorinobu as CEO, with V defeating Smasher. Hanako honours her deal with V and, after inserting an engram of Saburo into Yorinobu to avenge Saburo's murder, has Arasaka doctors extract the Relic from V. In all cases, it is revealed that the damage to V's body is irreversible. Depending on player choice, V either requests Arasaka upload them into Mikoshi until a suitable host body is found, remains in their body with an uncertain life expectancy, or allows Johnny to take over permanently (only achievable through attacking Arasaka). If V assaults Arasaka and chooses to remain in their body, they either become a Night City legend, or leave Night City with the Aldecaldos clan hoping to find a way to prolong their lifespan. If V surrenders their body to Johnny, the latter pays his respects to his friends and leaves Night City to start a new life.